

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
19 June 2003 (19.06.2003)

PCT

(10) International Publication Number
WO 03/050074 A1

- (51) International Patent Classification⁷: **C07C 217/74**,
213/10, 213/02, 253/30
- (21) International Application Number: PCT/IN02/00046
- (22) International Filing Date: 19 March 2002 (19.03.2002)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data:
1177/MUM/2001
13 December 2001 (13.12.2001) IN
- (71) Applicant: **CADILA HEALTHCARE LIMITED**
[IN/IN]; Zydus Tower, Satellite Cross Roads, Ahmedabad
380 015, Gujarat (IN).
- (72) Inventors: **RAMESHCHANDRA, Sonak, Bhavin**;
Cadila Healthcare Limited, 291, GIDC, Ankleshwar
393 002, Gujarat (IN). **PATEL, Mahesh, Shankarbhai**;
Cadila Healthcare Limited, 291, GIDC, Ankleshwar
393 002, Gujarat (IN). **PATEL, Gaurang, Balkrushna**;
Cadila Healthcare Limited, 291, GIDC, Ankleshwar 393
002, Gujarat (IN). **RAMAKRISHNA, Nirogi, Venkata,**
Satya; Cadila Healthcare Limited, Zydus Research Centre,
Sarkhej Bavla N.H. No. 8A, Moraiya Village, Ahmedabad
382 213 (IN). **MANAKIWALA, Satish, Champaklal**;
Cadila Healthcare Limited, 291, GIDC, Ankleshwar
393 002, Gujarat (IN). **AGARWAL, Virendra, Kumar**;
Cadila Healthcare Limited, 291, GIDC, Ankleshwar 393
- 002, Gujarat (IN). **PANDITA, Kanwal**; Cadila Healthcare
Limited, Zydus Tower, Sarkhej-Gandhinagar Highway,
Ahmedabad 380 015, Gujarat (IN). **PATEL, Pankaj,**
Ramanbhai; Cadila Healthcare Limited, Zydus Towers,
Sarkhej-Gandhinagar Highway, Ahmedabad 380 015 (IN).
- (74) Agents: **SUBRAMANIAM, Hariharan et al.**; Subrama-
niam, Nataraj & Associates, Patent & Trademark Attor-
neys, E-556, Greater Kailash-II, New Dehli 110 048 (IN).
- (81) Designated States (*national*): AE, AG, AL, AM, AT, AU,
AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU,
CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,
LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW,
MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG,
SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN,
YU, ZA, ZM, ZW.
- (84) Designated States (*regional*): ARIPO patent (GH, GM,
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW),
Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),
European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR,
GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent
(BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR,
NE, SN, TD, TG).
- Published:
— with international search report
- For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.

(54) Title: MANUFACTURE OF VENLAFAXINE HYDROCHLORIDE AND CRYSTALLINE POLYMORPHS THEREOF

(57) Abstract: The present invention discloses process for the preparation of ()-1-[2-(dimethylamino)-1-(4-methoxyphenyl)-ethyl] cyclohexanol hydrochloride (Venlafaxine hydrochloride) and its novel crystalline polymorphs designated as Form -I, Form -II, Form -III and crystalline forms of (R) and (S) enantiomers. These are characterized by specific Fourier Transform Infrared (FTIR), X-ray powder diffraction (XRPD) and Solid-state NMR (¹³C - CP/MAS NMR) and are useful as agents for treating depression.



WO 03/050074 A1

MANUFACTURE OF VENLAFAXINE HYDROCHLORIDE AND CRYSTALLINE POLYMORPHS THEREOF

5

BACKGROUND OF THE INVENTION

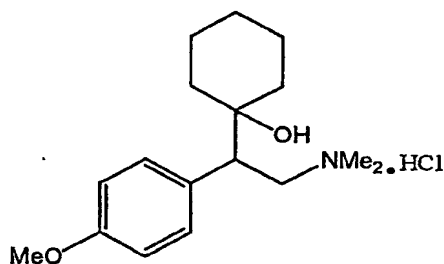
A number of nontricyclic antidepressants have recently been developed that diminish the cardiovascular and anticholinergic liability characteristic of tricyclic antidepressants. Some of these compounds are used as anti-obesity agents and have shown
10 promise in the treatment of cerebral function disorders such as parkinson's disease senile dementia. See, e.g., WO 94/00047 and WO/00114. The nontricyclic compound, Venlafaxine, chemically named (\pm) -1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl]-cyclohexanol, is an antidepressant which has been studied extensively and is described in, for example, U.S. Patent No.4761501 and Drugs of the Future 1988,13(9),839-840. Its
15 hydrochloride salt formulation is currently commercially available under the trade name *Effexor*. It is marketed in racemic form, which is a equal mixture of the (+) and (-) enantiomers of Venlafaxine and is indicated for the treatment of depression.

Although Venlafaxine contains an asymmetric carbon atom and is sold as a racemate, it has been reported that its (-) enantiomer is a more potent inhibitor of
20 norepinephrine synaptosomal uptake while its (+) enantiomer is more selective in inhibiting serotonin uptake. (Xenobiotica 1994,24(4), 315-327). Further more, studies have shown that the ratio of the two isomer's metabolism varies not only among species, but between subjects as well. (J.Clin.Pharmacol. 1992,32,716-724). In humans, Venlafaxine is transformed by a saturable metabolic pathway into two minor metabolites, N-desmethyl
25 Venlafaxine and N,O-didesmethylvenlafaxine, and one major metabolite, O-desmethyl Venlafaxine.

The present invention relates to the preparation of Venlafaxine hydrochloride which is known by the chemical name 1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl cyclohexanol hydrochloride useful as pharmaceutical agent and The racemic Venlafaxine
30 hydrochloride exhibit polymorphism, which we report herein for the first time. The polymorphs characterized are designated as Form - I, Form - II, and Form - III of racemic Venlafaxine hydrochloride and optically pure (R) and (S) enantiomers exhibit different crystalline structures as that of racemic Venlafaxine hydrochloride. The preparation of all the forms disclosed herein are described. The inter-conversion of different forms of racemic
35 Venlafaxine hydrochloride is also described herein.

U.S.patents 4535186, 4761501, 5043466; GB 2227743; CN 1225356, WO 00/59851, 00/32556; EP 112669 which are incorporated herein by references, describe

various processes and key intermediates for preparing racemic Venlafaxine hydrochloride while J. Med. Chem. 1990, 33, 2899-2905, and WO 00/32556 describe the preparation of racemic Venlafaxine and its resolution into (R) and (S) enantiomers. To the applicants' knowledge there is no polymorphic forms reported in literature on Venlafaxine hydrochloride.



Venlafaxine is prepared as its hydrochloride salt, i.e. 1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl]cyclohexanol hydrochloride salt (1:1). The hydrochloride salt is desirable since it enables Venlafaxine to be conveniently formulated in, for example, tablets, capsules, lozenges, powders, and the like for oral administration. Additionally, there is a need to produce Venlafaxine in a pure crystalline form to enable formulations to meet exacting pharmaceutical requirements and specifications.

Furthermore, the process by which Venlafaxine is produced needs to be one, which is amenable to large-scale production. Additionally, it is desirable that the product should be in a form that is readily filterable and easily dried. Finally, it is economically desirable that the product be stable for extended periods of time without the need for specialized storage conditions.

The applicants have now found that Venlafaxine can be prepared in different crystalline polymorphic forms. Thus, the present invention provides Venlafaxine hydrochloride in new crystalline forms designated as Form I, Form II, and Form III and crystalline forms of (R) and (S) Venlafaxine hydrochloride. Form I Venlafaxine consists of smaller particles having needle shape and exhibits slow filtration and drying characteristics in comparison with Form II and Form III.

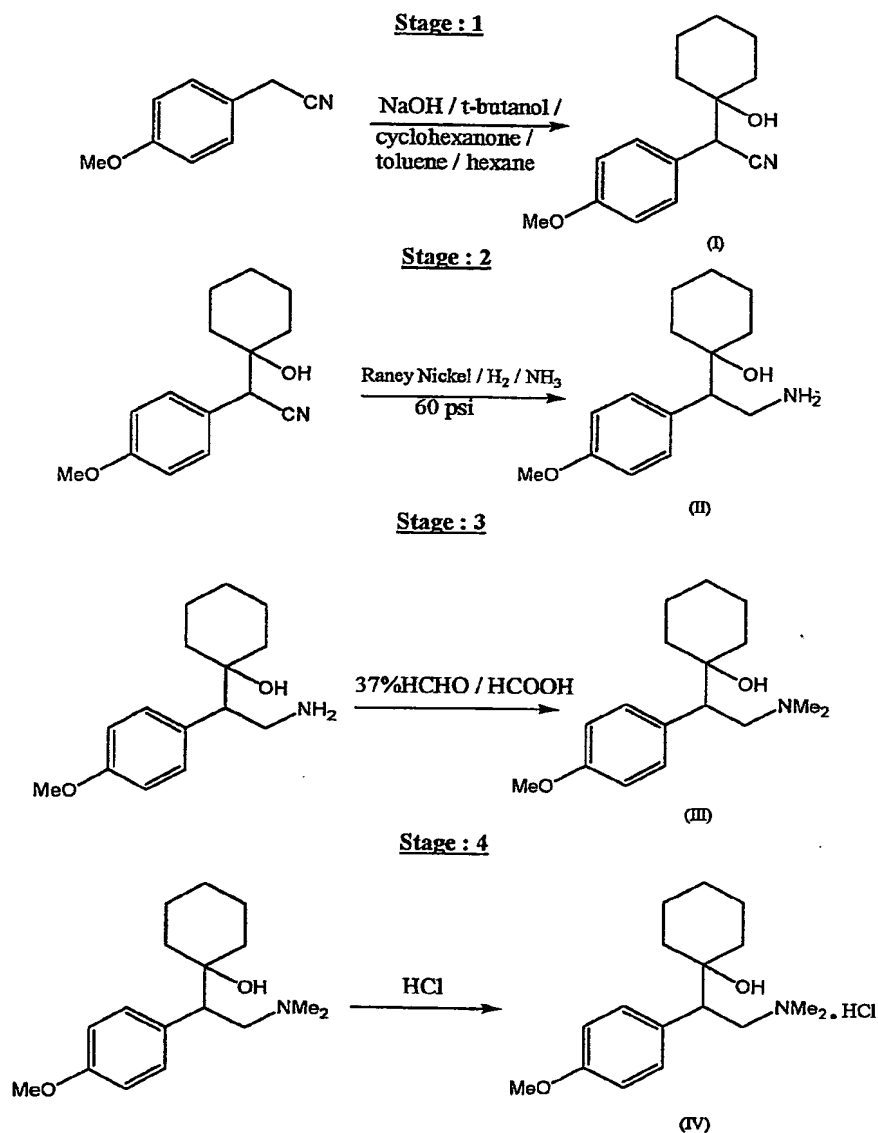
The reaction of p-methoxyphenyl acetonitrile with cyclohexanone takes place in the presence of n-butyl lithium or lithium diisopropylamide (US Patents 4535186, 4611078, 4761501, 5043466 and EP112669) to provide compound I while sodium methoxide, sodium amide or sodium hydride are mentioned in CN 1225356. All the above mentioned reagents are highly sensitive to moisture and air and catches fire. They are also very expensive.

In the 2nd stage the resulting compound I is hydrogenated over Rhodium supported on alumina to give primary amine derivative II. Again, in this stage Rhodium is very expensive and uneconomical on plant scale preparation.

The primary amine derivative (II) is methylated by formaldehyde and formic acid mixture to give Venlafaxine base (III) which is converted to the hydrochloride salt (Scheme 1)

SCHEME : 1

SYNTHETIC DIAGRAM OF VENLAFAXINE



Stage: - 1

Prior arts describe the method of condensation of cyclohexanone at the benzylic carbon of p-methoxyphenylacetonitrile employing n-butyl lithium or lithium diisopropylamide disclosed in US 4535186, US 4761501, US 5043466, WO 00/59851, and JMC 1990, 33, 2899, while in CN 1225356, sodium methoxide, sodium ethoxide, sodamide or sodium hydride are employed for the said conversion. All the above mentioned reagents and chemicals are highly sensitive to moisture and air and are unsafe and expensive on plant scale.

The present invention discloses the use of an inorganic base, which is abundantly available and relatively safe on commercial batches i.e. alkaline earth metal hydroxides like lithium hydroxide, sodium hydroxide and potassium hydroxide. Preferably, sodium hydroxide, which is the most economical and abundant chemical is used in present invention. In an improved methodology, in accordance with the present invention, the of sodium hydroxide flakes in n-hexane containing tert-butanol and p-methoxy phenylacetonitrile in a molar ratio of 3 : 1.1 : 1 respectively is reacted with a solution of cyclohexanone in a molar ratio of 1.1 in toluene at -5 to -10°C, after neutralizing sodium hydroxide with acetic acid, a white product is isolated from aqueous work up. The dried product accounts 74% yield based on p-methoxy phenyl acetonitrile having mp. 125 – 128°C (reported 123 – 126 °C) with high HPLC purity of 99.86%. The compound was further confirmed for the proposed structure as in scheme – I, stage - 1 by ¹H NMR, ¹³C NMR, & ESI-MS. The stage-1 compound prepared by this procedure matches in all tests such as mp, ¹H & ¹³C NMR, ESI-MS & HPLC with the one prepared by conventional procedures.

Stage: 2

Prior arts describe the method of reducing a cyano group to a aminomethyl group by employing Rhodium supported on alumina as a catalyst in hydrogenation procedure.

The present invention describes the use of Raney Nickel, Raney Copper and Raney Cobalt in the above reaction in place of expensive Rhodium metal. Raney nickel works well in such type of reductions. The use of Raney nickel in presence of anhydrous ammonia in hydrogenation is a well documented procedure. In an improved procedure, in accordance with the present invention, the reduction is carried out by employing hydrogenation reaction in an autoclave at 60 psi, containing Raney Nickel and anhydrous ammonia in methanol at 30°C. The reaction is over in 3-4 hrs showing the absence of starting material by TLC. The catalyst is filtered and the solvent is removed to provide a thick syrupy liquid with high purity of reduced product i.e. 93% in almost quantitative yield. HPLC analysis of reduced

product (II) shows main peak at 3.44 minute with two minor impurities appearing at 2.36 min. and at 23.92 minutes each 3 - 5% by area in HPLC.

Stage - 3

5 N-Methylation is achieved by standard procedure of Tilford and Van Campen modification (JACS., 1954, 76, 2431) employing aqueous formaldehyde and formic acid under reflux for several hours. The product is isolated as the syrupy liquid identified as Venlafaxine base (III) containing 82% pure Venlafaxine base accounting 75% yield of theoretical based on stage - 1 compound.

Stage-4

10 The Venlafaxine base thus obtained in stage 3 is subjected to hydrochloride formation by addition of anhydrous hydrochloric acid in isopropanol, in to a solution of Venlafaxine base in acetone at 5 to 10°C. The product is isolated as white crystalline material in a yield of 85% of theoretical having mp 210 to 212°C, with HPLC purity of 98% and HPLC assay 97%. This stage of operation removes the impurities present in
15 Venlafaxine base substantially.

Stage-5

The Venlafaxine hydrochloride obtained in stage 4 is refluxed with 10 volumes of isopropanol to get clear solution which is cooled to 5 to 10 °C and then filtered to get pure Venlafaxine hydrochloride with 90% recovery and HPLC purity of 99.60%, HPLC assay
20 98.4%, m.p. 215 to 216°C. This particular stage further improves the quality of Venlafaxine hydrochloride.

Stage - 6

The Venlafaxine hydrochloride thus obtained in stage - 5 is dissolved in methanol, treated with activated carbon, filtered, methanol is evaporated to dryness and the residue is
25 slurried in acetone and then refluxed and filtered at 5 to 10 °C to get purest Venlafaxine hydrochloride m.p 216 to 217 °C with 90% recovery, HPLC purity of the product is 99.8% and HPLC assay is 99%. The impurities level in this product is very low, each impurity being below 0.1%. Purest material is thus obtained in this stage which is employed to convert back into pure Venlafaxine base, which is then utilized to study various
30 polymorphic forms of racemic Venlafaxine hydrochloride.

The Venlafaxine base obtained in stage - 3 contains 82% pure Venlafaxine base, which on hydrochloride formation removes the impurities to a great extent. The Venlafaxine hydrochloride thus obtained is further purified two times to restrict each impurity to a concentration of less than 0.1% each in final purified Venlafaxine hydrochloride material.
35 The pure Venlafaxine hydrochloride thus obtained is converted into its pure Venlafaxine

base and all the preparations of different polymorphic forms of racemic Venlafaxine hydrochloride are achieved by using the pure Venlafaxine base. It is essential to employ material having highest purity to study polymorphism in right perspective because the product contaminated with impurities play a vital role in determining the outcome of crystalline forms, sometimes the presence of the impurities may provide wrong, non-reproducible and unpredictable crystallinity.

The pure Venlafaxine base thus obtained is subjected to hydrochloride formation in different solvents and under different reaction conditions. Such parameters play a major role in the formation of different polymorphs having different crystalline structures. The presence of co-solvents, the temperature at which hydrochloride formation occurs, refluxing the reaction mixture after hydrochloride formation, the temperature at which the filtration of hydrochloride salt is performed, all these factors mentioned above, determine the crystallinity of racemic Venlafaxine hydrochloride. It is evident from the experimental details that without changing basic solvent i.e. toluene, but changing the above mentioned parameters during hydrochloride formation all the three forms i.e. Form I, Form II and Form III of Venlafaxine hydrochloride are achieved.

Venlafaxine hydrochloride as obtained in stage 4 and 5 was found to be Form-I, the product obtained in stage 6 was found to be Form - II in well controlled laboratory conditions and to the applicants' surprise under exactly similar conditions Venlafaxine hydrochloride was found to have totally different crystalline form designated as Form - III on plant scale.

The effect of co-solvent was also studied in conversion of Form I to Form - II or Form - III. For example, Venlafaxine hydrochloride Form - I is dissolved in methanol which is removed completely by distillation, but since, it is not possible all the time to remove methanol completely, the product is refluxed in acetone, cooled and filtered. Experimental details reveal that methanol, even in concentration of 5 - 10 % in acetone, does not affect the polymorphism. Even absence of methanol does not affect the polymorphism in all cases and Form - I is converted into Form - II or Form - III completely.

When stage - 6 is attempted on 40 to 50 kg scale on plant, it was surprisingly found that a new polymorph designated as Form - III is formed under similar conditions of operations while Form - II is achieved in laboratory trials under same conditions. Thus, the applicants now conclude that the design and rpm of agitator play a vital role in the formation of the polymorph, which is totally distinguishable and different from polymorph - II, which is obtained in laboratory under well controlled conditions. In further studies

Form – II or Form – III is converted into Form I by dissolving in hot isopropanol and cooling to 5 to 10°C then filtering and drying.

The applicants have found that Form – I is always with small particle size and is therefore, relatively slow in filtration and drying as compared to Form – II or III which have higher particle size with better filtration and drying characteristics.

Surprisingly, however, when the applicants attempted to explore whether polymorphic forms can be prepared starting from optically pure R- and S- Venlafaxine hydrochloride also, it was found that no polymorphism was observed in chiral Venlafaxine hydrochloride as revealed by DSC, X-ray powder diffraction. The above data is totally different as observed in three forms of racemic Venlafaxine hydrochloride. Due to higher melting point of chiral R- or S- Venlafaxine hydrochloride (240 to 242°C) as against mp of 214 – 216° of three forms of racemic Venlafaxine hydrochloride. R- & S- Venlafaxine hydrochloride exhibit well defined crystalline patterns as evidenced from XRPD.

The present invention thus indicates that equal mixture of R- and S- Venlafaxine hydrochloride in racemic Venlafaxine hydrochloride is the key factor to crystallize the material in different crystalline polymorphic forms.

It was also attempted in the present invention to interconvert the crystallinity in chiral R- & S- Venlafaxine hydrochloride in different solvents and under different reaction conditions, but there was no change in the original crystallinity confirming our belief that the existence of polymorphism in racemic Venlafaxine hydrochloride is due to the presence of both the enantiomers in equal amounts. It is therefore, believed that R- enantiomer is an impurity to S- enantiomer and vice versa, which gives rise to polymorphism in racemic Venlafaxine hydrochloride not in chiral Venlafaxine hydrochloride.

Since Venlafaxine hydrochloride is marketed as racemic, polymorphism is to be dealt with great care, especially since the Form which is more thermodynamically stable with desired bioavailability would be preferred over other Forms considering storage conditions and shelf life. Less thermodynamically stable Form is prone to convert into stable Form and such Forms are not good candidates for pharmaceutical applications, since this conversion will be noticed during the storage of the material.

Stage – 7

Pure racemic Venlafaxine hydrochloride thus obtained in stage - 6 is converted to pure racemic Venlafaxine base as a white solid in quantitative yield having melting point 80 °C by usual procedures.

Stage – 8

The pure Venlafaxine base thus obtained in stage - 7 is subjected to hydrochloride formation in (i) ethyl acetate (ii) acetonitrile (iii) acetone (iv) isopropanol (v) MIBK and (vi) toluene by passing dry hydrogen chloride gas at 0 to 5°C except in isopropanol, where a solution of dry hydrogenchloride gas in isopropanol is used. After the completion of hydrochloride formation the product is filtered and washed with same solvents, the product is dried at 60°C till constant weight. The product Venlafaxine hydrochloride obtained from (i) ethyl acetate (ii) acetonitrile (iii) acetone (iv) isopropanol (v) MIBK (vi) toluene were found to be Form - I. But after passing HCl gas at 25 to 30 °C, the mixture is heated to reflux. On cooling Form - II is obtained except in case of isopropanol where Form - I is obtained.

Stage - 9

The six steps as conducted in stage - 8 were repeated instead of dry hydrogenchloride gas, a solution of dry hydrogenchloride gas in isopropanol were added at 30 to 35°C and the reflux was maintained in all the experiments for 1 hour except in isopropanol where complete dissolution occurred in 5 minutes. In all the steps, the reactants were cooled to 30 to 35°C and then filtered and dried. To the applicants' surprise Form - I is achieved only in isopropanol, while acetone, ethyl acetate, acetonitrile and MIBK produced Form - II. It can therefore, be concluded from stage - 8 and stage - 9 that the temperature and solvent play a vital role in determining the polymorphic forms of the Venlafaxine hydrochloride. As shown earlier in stage 6 during manufacturing Venlafaxine hydrochloride on plant scale and during interconversion of Form - I to Form - II or Form II to I on plant scale only Form III is obtained. A number of experiments were carried out to prepare Form III in laboratory i.e., 5 to 10g batch size. Fortunately, success was achieved when Venlafaxine base in toluene was treated with IPA/HCl gas at 30 - 35°C and then heated to reflux. On cooling and drying the material surprisingly the Venlafaxine hydrochloride obtained contains Form III crystallinity. While when dry HCl gas is passed into a solution of Venlafaxine base in toluene at 0 - 5 °C on work up Form I is obtained, if the solution heated to reflux on work up Form - II is obtained. This example again support our believes that the solvent, co-solvent and temperature plays an important role in the formation of different crystallinity.

Stage - 10

The Venlafaxine hydrochloride Form - II or III is dissolved in methanol and treated with activated carbon, filtered through hyflow bed and methanolic solution of Venlafaxine hydrochloride is evaporated to dryness and acetone is added to the dried mass and refluxed for 1 hour with stirring, cooled to 30 to 35°C, filtered and dried. Four experiments were

carried out, in one of the experiments, after removal of methanol completely the product was recovered without any addition of acetone, the product was found to be Form - II. Remaining three experiments were designed in such a way that before filtration of final product methanol content was (i) nil (ii) 5% (iii) 10% with respect to acetone content, the product Venlafaxine hydrochloride obtained from these three experiments were found to be again Form - II. Form - II is recovered as such while Form - III is converted into Form - II in laboratory trials.

Stage - 11

Venlafaxine hydrochloride Form II or Form III is converted into Form - I by dissolving Form II or Form III in hot isopropanol, cooling to 5 to 10°C then filtering and drying till constant weight.

Stage - 12

Venlafaxine hydrochloride Form - I is converted into Form II or Form III by dissolving Form I in methanol, evaporating the solvent, refluxing with acetone, cooling to 5 to 10°C, filtering and drying. Under identical conditions of operations, Form II is achieved in laboratory trials, whereas plant scale batches produced Form III. Stage - 13

Racemic Venlafaxine base is resolved into enantiomeric pure (R) and (S) Venlafaxine base by known procedures. Both the enantiomers were subjected to hydrochloride formation in different solvents and under different experimental conditions. Stage - 13 reactions demonstrated that the products obtained were similar to each other in all the aspects i.e. melting point, DSC, and X-ray powder diffraction data, thereby confirming the occurrence of only one crystalline form in (R) and (S) Venlafaxine hydrochloride which is obviously different from Racemic Venlafaxine hydrochloride Form I, II and III due to the difference in melting point of racemic Venlafaxine hydrochloride (214 to 216°C) and (R) and (S) Venlafaxine hydrochloride (240 to 242°C). Moreover (R) and (S) Venlafaxine hydrochloride completely match with each other on the above data as mentioned.

Stage - 14

The interconversion of crystallinity of (R) or (S) Venlafaxine hydrochloride was attempted in isopropanol where racemic Venlafaxine hydrochloride Form - II or III is converted into Form - I, but it was found that the (R) or (S) Venlafaxine hydrochloride was recovered as such and therefore no change in original crystallinity of (R) or (S) Venlafaxine hydrochloride was noticed.

CHARACTERIZATION OF VENLAFAXINE HYDROCHLORIDE POLYMORPHIC FORMS:

Crystalline Form-I, Form-II and Form-III racemic Venlafaxine Hydrochloride were characterized by Fourier Transform Infrared (FTIR) spectra, X-ray Powder diffraction patterns (XRPD) and Solid-state ^{13}C Nuclear Magnetic Resonance Spectrum (^{13}C - CP/MAS NMR).

Fourier Transform Infrared Spectrum (FTIR):

Fourier transform infrared spectra of the polymorphs were acquired on an Shimadzu FTIR-8300 spectrometer equipped with diffused reflectance accessory. FTIR spectra of the three polymorphs in the region $400\text{--}4000\text{ cm}^{-1}$ at a resolution of 2 are shown in Figs. 1-3. While many of the spectral features are broadly similar, there are discernible differences between the three forms which can be used to distinguish and indentify the individual Forms. No attempt was made to assign all the observed modes in the FTIR spectra. Form-I showed greater multiplicity when compared with the other two Forms. Table-1 lists the wave numbers in the region of $500\text{--}1700\text{ cm}^{-1}$ of the three polymorphs.

Table-1: FTIR wave numbers (cm^{-1}) of racemic Venlafaxine hydrochloride

FTIR spectral wave numbers, cm^{-1}		
Form-I	Form-II	Form-III
501.5	526.5	526.5
522.7	545.8	545.8
553.5	594.0	592.1
580.5	634.5	634.5
634.5	667.3	667.3
657.7	734.8	734.8
667.3	769.5	769.5
719.4	817.8	817.8
740.6	829.3	829.3
767.6	858.3	844.8
777.3	908.4	858.3
810.0	927.7	908.4
837.0	958.6	927.7
908.4	970.1	958.6
927.7	981.7	970.1
956.6	1018.3	981.7
970.1	1037.6	1018.3
1016.4	1060.8	1037.6
1041.5	1080.1	1060.8

1062.7	1107.1	1080.1
1082.0	1139.9	1107.1
1109.0	1153.4	1139.9
1139.9	1178.4	1153.4
1153.4	1242.1	1178.4
1178.4	1274.9	1242.1
1247.9	1303.8	1274.9
1274.9	1365.5	1303.8
1305.7	1386.7	1365.5
1317.3	1404.1	1386.7
1367.4	1440.7	1404.1
1384.8	1473.5	1440.7
1400.2	1512.1	1473.5
1438.8	1581.5	1512.1
1471.6	1612.4	1581.5
1514.0		1612.4
1581.5		
1614.3		

X-Ray Powder Diffraction (XRPD):

X-ray powder diffraction patterns were recorded using Rigaku Multiflex automated
 5 X-ray diffractometer with CuK α radiation (30 mA, 40 KV, $\lambda = 1.5406$ Å). Slits I, II are 1° and Slits II at 0.15 mm and IV at 0.6 mm.

The silicon standard was run each day to check the x-ray tube alignment. Continuous $\theta/2\theta$ coupled scan: 4.00 ° to 40.00 ° in 2θ at a scan rate of 4°/min. Sample tapped out of vial and pressed onto zero background quartz sample holder. Sample width
 10 7.5 x 6.5 mm with 0.5 mm depth. Samples are stored and run at room temperature.

Table-2, 3 & 4 lists the 2θ , d-spacings and relative intensities of all lines in the XRPD with RI of >10% for Form-I and Form-II and >5% for Form-III respectively. It should be noted that computer-generated, unrounded numbers are listed in these tables. The X-ray powder diffractograms of the three polymorphic Forms of racemic Venlafaxine
 15 hydrochloride are given in Figs. 4, 5 & 6, and diffractograms of R(+) Venlafaxine hydrochloride and S(-) Venlafaxine hydrochloride are given in Figs. 7 & 8 respectively. The three polymorphic forms of racemic Venlafaxine hydrochloride can be easily differentiated from each other and also individually can be identified from their x-ray powder diffractograms and diffraction data. The diffractograms of R(+) Venlafaxine
 20 hydrochloride and S(-) Venlafaxine hydrochloride are very similar to each other and represent the same crystalline structure to both chiral enantiomers of Venlafaxine hydrochloride.

Table-2: XRPD data of racemic Venlafaxine hydrochloride Form-I

2 θ	d-value	Relative Intensity (>10%)
6.790	13.007	22
8.410	10.505	16
10.270	8.606	15
12.750	6.937	57
13.540	6.534	38
15.420	5.741	11
15.580	5.682	21
15.620	5.668	20
15.740	5.625	12
16.310	5.430	14
16.350	5.417	16
16.800	5.272	10
18.990	4.669	23
19.790	4.482	10
20.350	4.360	100
21.240	4.179	35
21.820	4.069	26
25.040	3.553	14
25.090	3.546	20
25.150	3.538	14
27.220	3.273	10
27.270	3.267	10
28.470	3.132	10
28.560	3.122	13
28.610	3.117	13
31.090	2.874	10
31.590	2.829	11
31.650	2.824	10
31.720	2.818	10
33.990	2.635	10
35.120	2.553	18
35.230	2.545	17

Table-3: XRPD data of racemic Venlafaxine hydrochloride Form-II

2 θ	d-value	Relative Intensity (>10%)
6.690	13.201	23
10.210	8.656	46
13.450	6.577	34
15.310	5.782	28
15.380	5.756	39
15.520	5.704	53

18.140	4.886	25
18.170	4.878	26
19.610	4.523	14
19.680	4.507	21
20.260	4.379	100
21.460	4.137	13
21.580	4.114	33
21.650	4.101	46
21.710	4.090	46
22.570	3.936	13
22.650	3.922	15
25.490	3.491	10
25.540	3.484	11
27.160	3.280	11
28.020	3.181	11
28.100	3.172	12
28.180	3.164	12
28.210	3.160	11
34.970	2.563	19
35.060	2.557	25

Table-4: XRPD data of racemic Venlafaxine hydrochloride Form-III

2 θ	d-value	Relative Intensity (> 5%)
6.730	13.123	15
10.240	8.631	8
13.490	6.558	28
15.370	5.760	6
15.410	5.745	7
15.480	5.719	8
15.560	5.690	8
18.180	4.875	6
18.220	4.865	5
20.180	4.396	30
20.300	4.371	100
21.600	4.110	7
21.650	4.101	9
21.740	4.084	13
27.200	3.275	13
27.260	3.268	6
35.090	2.555	10
35.180	2.548	6

5 **Solid-state ^{13}C Nuclear Magnetic Resonance Spectrum**
(^{13}C - CP/MAS NMR):

Solid-state ^{13}C Nuclear magnetic resonance spectra were acquired on Bruker DRX 500 spectrometer at a resonance frequency of 125.77 MHz for ^{13}C and 500 MHz for ^1H using the Cross-polarization (CP) with magic-angle spinning (MAS) technique. Approximately 200 mg of each polymorph was used in the acquisition of their respective spectra. All measurements were made at ambient temperature. The chemical shifts were referred to the CH carbon of a spinning sample of adamantane taken as 37.8 ppm from TMS. A contact time of 1 milli second and relaxation delay of 5 sec was used. The data were collected at a spinning speed of 8.0 KHz for each sample. A positive assignment of the origin of signal multiplicities in the spectra require additional ^{13}C CP/MAS NMR experiments to be performed at a lower static field strength and also at varying temperature. No detailed attempt was made to assign all the resonance frequencies and signal multiplicities.

Figs-9, 10 & 11 shows the ^{13}C CP/MAS NMR spectra of the three polymorphs respectively and the Table-5 shows all the resonances for all three Forms.

Table-5: Solid-state ^{13}C Chemical shifts (ppm) of racemic Venlafaxine hydrochloride Form - I, II and III.

^{13}C Chemical shifts (ppm)		
Form-I	Form-II	Form-III
221.52	221.28	221.27
197.24	198.23	198.25
196.76	196.18	196.20
193.64	194.37	194.37
179.11	181.35	181.38
171.72	172.33	172.32
157.90	157.65	157.66
133.62	134.62	134.65
133.14	132.58	132.59
130.04	130.75	130.79
115.49	117.74	117.77
108.10	108.71	108.74
94.26	94.03	94.04
74.11	73.89	73.93
69.99	71.00	71.01
69.51	68.94	68.97
66.40	67.11	67.15
59.36	59.23	59.30
54.81	55.59	55.63
51.84	54.13	54.17
50.99	51.32	51.36

44.45	45.08	45.09
43.40	43.29	43.33
42.37	41.49	41.53
37.80	37.80	37.85
35.69	25.94	26.00
25.52	23.74	23.84
21.74	21.40	21.45

Transmission microscopy pictures:

Transmission microscopy pictures were taken using OPTIMA Binocular research microscope with a magnification of 100X.

SUMMARY OF THE INVENTION

The improved process of manufacturing racemic Venlafaxine hydrochloride is described in scheme – 1. Basic starting material and intermediates remain as disclosed in the above mentioned patent procedures, the difference lies in the use of simple, safe and economical reagents as disclosed in following stages.

Venlafaxine Hydrochloride is prepared by the improved method shown in scheme – I

- Stage - I: p-Methoxyphenylacetonitrile is reacted with cyclohexanone in presence of alkali metal hydroxide in a mixture of toluene and hexane.
- Stage - II: Compound I is hydrogenated over Raney Nickel in the presence of anhydrous ammonia.
- Stage - III: The primary amine II is methylated by formaldehyde and formic acid to give Venlafaxine base.
- Stage - IV: The base is converted to the hydrochloride salt i.e. Venlafaxine hydrochloride in acetone and anhydrous hydrogen chloride in isopropanol to give polymorph - I.
- Stage - V: Venlafaxine hydrochloride is purified in isopropanol to give polymorph - I.
- Stage - VI: Venlafaxine hydrochloride is treated with activated carbon in methanol, solvent is evaporated to dryness, residue is slurried in acetone, cooled to 25 to 30°C, then filtered and dried to a constant weight to give polymorph - II in laboratory and polymorph - III on plant scale.
- Stage - VII: Venlafaxine hydrochloride is converted into free Venlafaxine base.
- Stage - VIII & IX: Pure Venlafaxine base is subjected to hydrochloride formation in (i) ethyl acetate (ii) acetonitrile (iii) acetone (iv) isopropanol, (v) MIBK and (vi) toluene hydrochloride preparation at 0 to 5°C provides only polymorph

- I in above mentioned solvents, whereas in same solvents hydrochloride formation is being carried out at 25 to 30°C, then refluxed, cooled to 25 to 30°C then filtered and dried to a constant weight, polymorph - I is achieved only in isopropanol, whereas ethyl acetate, acetonitrile acetone and MIBK provides Form - II. Form - III is obtained when toluene is used as solvent.

5 Stage - X: Polymorph - III is converted into polymorph - II in laboratory conditions whereas polymorph - II is unaffected.

Stage - XI: Form - II or Form - III is converted into Form - I in hot isopropanol.

10 Stage - XII: Form - I is converted into Form - II in laboratory conditions while Form I is converted into Form - III on plant scale. The effect of cosolvent methanol is also studied in acetone, in laboratory trials, the presence (methanol content nil to 10%) doesn't effect the polymorphism, in all cases polymorph - II is achieved.

15 Stage - XIII: (R) and (S) enantiomers of Venlafaxine hydrochloride are prepared, both the enantiomers are crystalline structure, melting point of both are higher than racemic Venlafaxine hydrochloride Form - I, Form - II and Form - III and consequently they differ on DSC and X-ray powder diffractogram. No polymorphism was found to occur in (R) and (S) Venlafaxine hydrochloride.

20 Stage - XIV: The interconversion of crystallinity of (R) and (S) enantiomers of Venlafaxine hydrochloride was attempted in hot isopropanol, the material was recovered as such, further confirming the absence of polymorphism in (R) and (S) Venlafaxine hydrochloride.

25 The invention is further described by the following non-limiting examples which refer to the accompanying Figs. 1-14, brief particulars of which are given below:

Fig - 1: Fourier Transform Infrared (FTIR) spectrum of racemic Venlafaxine hydrochloride Form-I

30 Fig - 2: Fourier Transform Infrared (FTIR) spectrum of racemic Venlafaxine hydrochloride Form-II

Fig - 3: Fourier Transform Infrared (FTIR) spectrum of racemic Venlafaxine hydrochloride Form-III

35 Fig - 4: X-ray Powder Diffractogram of racemic Venlafaxine hydrochloride Form-I (X-axis: 2θ and Y-axis: intensity)

40 Fig - 5: X-ray Powder Diffractogram of

- racemic Venlafaxine hydrochloride Form-II
(X-axis: 2θ and Y-axis: intensity)
- 5 Fig - 6: X-ray Powder Diffractogram of
racemic Venlafaxine hydrochloride Form-III
(X-axis: 2θ and Y-axis: intensity)
- 10 Fig - 7: X-ray Powder Diffractogram of
R(+) Venlafaxine hydrochloride
(X-axis: 2θ and Y-axis: intensity)
- 15 Fig - 8: X-ray Powder Diffractogram of
S(-) Venlafaxine hydrochloride
(X-axis: 2θ and Y-axis: intensity)
- Fig - 9: Solid-state ^{13}C nuclear magnetic resonance spectrum of racemic Venlafaxine
hydrochloride Form-I
(X-axis: chemical shift, ppm and Y-axis: intensity)
- 20 Fig - 10: Solid-state ^{13}C nuclear magnetic resonance spectrum of racemic Venlafaxine
hydrochloride Form-II
(X-axis: chemical shift, ppm and Y-axis: intensity)
- 25 Fig - 11: Solid-state ^{13}C nuclear magnetic resonance spectrum of
racemic Venlafaxine hydrochloride Form-III
(X-axis: chemical shift, ppm and Y-axis: intensity)
- 30 Fig - 12: Transition microscopy picture of
racemic Venlafaxine hydrochloride Form-I
- Fig - 13: Transition microscopy picture of
racemic Venlafaxine hydrochloride Form-II
- 35 Fig - 14: Transition microscopy picture of
racemic Venlafaxine hydrochloride Form-III

Example - 1

Preparation of 1-[cyano(4-methoxyphenyl)methyl]cyclohexanol :

40 In a 5 lit reaction vessel, n-hexane 2250 ml, caustic soda 204 g and *tert.* butanol 138 g were charged and stirred for 1 hr at 25 - 30°C and then cooled to -5 to -10°C. To this a solution of 250 gm p-methoxyphenyl acetonitrile in 250 ml toluene was slowly added in 45 minutes at -5 to -10°C. The mass was stirred at -10°C for 45 minutes and then a solution of
45 183 g cyclohexanone in 183 ml toluene was added in 45 minutes. The reaction mass was further stirred at -5°C to -10°C for 4 hours and the reaction progress was monitored by TLC. The reaction mass was dumped slowly in 2400 ml ice-water containing 300 ml acetic acid with cooling. Which was stirred for 30 min. at 15 to 20 °C. The product was filtered

and thoroughly washed with water. The product was dried at 70 °C to give 307 gm dry material yield, 74% of theoretical based on p-methoxyphenyl acetonitrile, having melting point 125 to 128 °C reported (123 to 126 °C).

5 **Example - 2**

Preparation of 1-[2-Amino-1-(4-methoxyphenyl)ethyl] cyclohexanol.

1-[cyano(4-methoxyphenyl)methyl] cyclohexanol (300 g) was dissolved in 4500 ml
10 methanol containing 150 g ammonia to this 150 g Raney nickel was added and hydrogenated at 60 psi pressure for 4 hrs. The catalyst was filtered through hyflowbed and the filtrate was evaporated to get an oil (300 gm). HPLC purity showed the material to be 93% pure.

Example - 3

15

Preparation of 1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl] cyclohexanol:

A solution containing 1-[2-amino-1-(4-methoxyphenyl)ethyl]cyclohexanol (275 g),
88% formic acid (867 g), 30% aqueous formaldehyde (624 g) and water (750 ml) was
20 refluxed for 14 hrs. The solution was cooled to 15 °C and was basified with 40% NaOH and extracted with chloroform. (3 x 800ml + 2 x 150 ml). The extract was evaporated to a residue wt. :270 g.

Example - 4

25

Preparation of 1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl] cyclohexanol Hydrochloride: [Form - I]

The residue (50 g) as obtained in example - 3 is dissolved in 15 times acetone and
30 to this, a solution of isopropanolic hydrochloride was added to bring the pH = 2 at 5 to 10 °C the precipitated material was filtered and washed with isopropanol and dried till constant weight of 37 gm, melting point 210 to 212 °C.

Example - 5

35

Purification of 1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl] cyclohexanol Hydrochloride: [Form - I]

35 gm Venlafaxine hydrochloride as obtained in example - 4 was dissolved in 10
40 volumes of hot isopropanol and cooled to 5 to 10 °C, the precipitated material was filtered

and washed with isopropanol, dried till constant weight of 29 to 30 gm pure material, melting point 215 to 217°C.

Example - 6

5

Preparation of 1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl] cyclohexanol Hydrochloride: [Form - II]

25 gm Venlafaxine hydrochloride as obtained in example - 5 is dissolved in 100 ml methanol at 25 to 30°C, 2 g carbon was added stirred for 30 min. filtered through hyflowbed, 2 x 15 ml methanol washed are given to the bed. Then methanol was distilled completely in vacuum. The traces of methanol are removed by adding 25 ml acetone and distilled completely. The process was repeated. Then 75 ml acetone was added to the residue, refluxed for 30 minutes, stirred 10 min at 30 °C, cooled to 5 to 10 °C, filtered and washed with acetone 2 x 25 ml, the product was dried till constant weight of 23 gm.

Example - 7

Preparation of Venlafaxine base (pure):

150 gm pure Venlafaxine hydrochloride as obtained in example 5 was dissolved in 300 ml D.M.Water and cooled to 10°C, the pH ≈ 10, was adjusted by adding 20% aqueous sodium hydroxide solution. It was then extracted with chloroform (3 x 200 ml) and the chloroform, the extracts are combined and was washed with D.M.Water (150 ml), chloroform was evaporated to a oily residue, (weight = 128 gm), which was solidified at 25 to 30°C.

Preparation of Venlafaxine hydrochloride Form - I

Example - 8

30

10 g of Venlafaxine pure base was obtained in example 7 is dissolved in 100 ml isopropanol at 25 - 30°C, the solution was cooled to 0 to 5°C, 10 ml solution of dry HCl gas in isopropanol was slowly added (to get pH ≈ 2 of the reaction mix). During addition white materials of Venlafaxine hydrochloride was separated. Stirred 1 hr. at 0 - 5 °C, the solid was filtered washed with isopropanol dried at 60 °C, dry wt. = 9 g.

Example - 9

10 g of Venlafaxine base (pure) was stirred with 100 ml acetonitrile at 25 to 30°C to get clear solution. It was cooled to 0 to 5°C, and dry HCl gas was passed to get pH of the solution 2. During the gas passing, precipitation of solid was started. The reaction mixture

was further stirred for 1 hr. at 0 – 5 °C, filtered and washed with acetonitrile. dry at 60 °C till constant weight of 7.5 g.

Example – 10

5 10 g of Venlafaxine base (pure) was stirred with 100 ml ethyl acetate at 25 to 30 °C to get clear solution. It was cooled to 0 to 5 °C, and dry HCl gas was passed to get pH of the solution 2. During the gas passing precipitation of solid was started which is further stirred for 1 hr. at 0 – 5 °C, filtered and washed with ethyl acetate, and dried at 60 °C till constant weight of 10.5 g.

10 **Example – 11**

15 10 g of Venlafaxine base was dissolved in 100 ml acetone at 25 to 30 °C then cooled to 0 – 5 °C, dry HCl gas was passed till pH 2, which is further stirred for 1 hr at 0 – 5 °C, filtered, washed with chilled acetone and dried at 60 °C, till constant weight of 9.8 gm was achieved

Example – 12

20 5 gm of Venlafaxine base was dissolved in 50 ml MIBK at 30 to 35 °C then cool to 0 to 5 °C. To this with stirring a solution of HCl gas in IPA was added to bring pH ~ 2 of the reaction mixture. The product precipitate was stirred for 1 hr at 0 to 5 °C and worked up to give 4.7 gm product.

Example – 13

25 10 gm of Venlafaxine base (pure) was stirred with 100 ml isopropanol. To this a solution of dry HCl gas in isopropanol (16% w/v) (10 ml) was dropwise added at 25 to 30 °C to get pH of the reaction mass 2. It was then heated to 64 °C to dissolve the solid stirred 5 min. at this temp. and then slowly cooled to 30 °C and filtered. The solid was washed with isopropanol and dried at 60 °C till constant weight of 6.8 g was achieved.

30

Example – 14

35 Venlafaxine crude base (84.3 gm) obtained from stage 3 was dissolved in 1260 ml of acetone at 25 to 30 °C then cool to 5 to 10 °C. A solution of dry HCl gas in isopropanol was slowly added at 5 to 10 °C till the pH of the mass = 2 was obtained. The product precipitated was stirred 1 hr. at 5 – 10 °C filtered and washed with acetone The wet material was dried at 60 °C to a constant weight. Dry weight = 62 gm.

Example – 15

Venlafaxine HCl 50 g (Form – III) and isopropanol 250 ml were heated slowly in 500 ml R. B. flask at 80 to 85 °C, to get a clear solution, refluxed for 1 hr (85 °C) slowly cooled to 50 °C, and then cooled to 30°C stir for 1 hr. at r.t., filtered, washed with isopropanol, dried at 60 °C, dry weight = 45.6 g.

Example – 16

Venlafaxine . HCl (Form – II) 5 gm (ven-4/18/145) in 75 ml isopropanol was heated to 70°C to dissolve the solid, stirred for 5 min. at 70°C, then cooled to 25 to 30 °C, stirred for 1 hr. at 25 to 30°C, filtered, washed with isopropanol and dried at 60°C, to obtain dry 3.8 g product.

15 Preparation of Venlafaxine hydrochloride Form – II**Example – 17**

Venlafaxine base Pure – 10 g was dissolved in 100 ml acetone at 25 to 30°C. To this solution dry HCl gas was passed till the pH of the solution ~ 2 was attained. It was then heated to reflux and refluxed for 5 min., cooled to 25 to 30°C, filtered the solid and washed with acetone dried at 60°C. Product with dry weight = 9.3 gm was obtained.

Example – 18

Example 17 is repeated by using 100 ml of ethyl acetate instead of acetone with reflux time for 1 hr., dried at 60°C. Dry weight of the product was 10.1 gm.

Example – 19

Example 18 was repeated by using 100 ml acetonitrile as solvent and dried at 60°C. Dry weight of the product was 5.8 gm.

Example – 20

5 gm Venlafaxine base was dissolved in 50 ml MIBK at 30 to 35 °C. To this with stirring was added a solution of HCl gas in IPA till pH ~ 2 is achieved. Thereafter, the temperature was raised to reflux and maintained reflux temperature for 1 hr. and then cooled to 30 °C. Thereafter, it was stirred for 1 hr at 30 to 35 °C, filtered, washed with MIBK and dried at 60 °C. 4.7 gm product is obtained.

Example – 21

Venlafaxine.HCl (Mix. of Polymorph I + II) (pure)– 25 g was dissolved in 100 ml methanol at 25 to 30°C. 2 g carbon was added stirred for 30 min. filtered through hyflowbed. 2 x 15 ml methanol wash were given to the bed. Then methanol was distilled completely in vacuum. The traces of methanol were removed by adding 25 ml acetone and distilled completely. The process was repeated. Then 75 ml acetone was added to the residue, reflux and cool upto 25 to 30°C. Stirred 10 min at 30 °C, filtered and washed with acetone 2 x 25 ml, dried at 60°C, dry weight = 23 gm.

Example – 22

Following four trials were taken as per example 21. After distillation of methanol the reaction mass was analyzed by GC for % methanol and % methanol was adjusted as per following table. Distillation of acetone which removes methanol by azeotropic distillation was omitted.

	% in methanol reaction	Input	Output
a)	Nil	Form III	Form II
b)	5%	Form III	Form II
c)	10%	Form III	Form II
d)	After methanol distillation the solid is scrapped and dried.	Form III	Form II

Example – 23

5 gm Venlafaxine base was dissolved in 50 ml toluene at 30 to 35 °C. To this, while stirring was added dry HCl gas till pH ~ 2 was achieved at 30 to 35 °C. The temperature was thereafter raised to reflux and maintained at reflux temperature for 1 hr then cooled to 30 °C, stirred for 1 hr at 30 to 35 °C filtered and washed with toluene and dried at 60 °C. Dry weight of the product obtained was 5.3 gm.

Example – 24

Example 23 was repeated by using MIBK as a solvent, which gave 5.2 gm material.

Preparation of Venlafaxine hydrochloride Form – III

It was surprisingly noted that in a manufacturing procedure of Venlafaxine hydrochloride on plant level, always Form – III was obtained in all the plant batches consistently.

Example – 25

5 g of Venlafaxine base was dissolved in 50 ml toluene at 30 to 35 °C. To this with stirring, a solution of HCl gas in IPA was added to get pH ~ 2 of the reaction mixture. It was refluxed for 1 hr (85 to 90 °C, cooled to 30 to 35 °C and stirred 1 hr at 30 to 35 °C. On work up, the solid obtained was dried at 60 °C to give 4.7 gm product.

Preparation of Venlafaxine hydrochloride chiral Form:**Example – 26**

Venlafaxine base (pure) racemic (40 g) was dissolved in 300 ml ethyl acetate. To this with stirring a solution of di-p-tolyl-L-tartaric acid (32 g) in ethyl acetate (240 ml) was slowly added in 30 min. at 25 to 30°C, stirred for 4 hrs more at 25 to 30°C. The solid was filtered and washed with 2 x 40 ml ethyl acetate. The filtrate was stored for the isolation of (R) enantiomer. The solid, weighing 40 gm, was dried at 55 to 60 °C. The dry wt. of the product was = 38 gm and the melting point was 116 to 120 °C. Sp. Rotation = -60.2971 (c = 1.0 methanol).

Example – 27

35 g of the salt of example – 26 was refluxed with 490 ml ethyl acetate and 35 ml methanol for 30 min. slowly cooled to 25 to 30°C, stirred 1 hr. at 25 to 30°C, filtered, washed with ethylacetate 2 x 35 ml. and dried at 60 °C, to a constant weight dry wt. = 26 gm, melting point 120 to 125°C. Sp. Rotation = -58.7565 (c = 1.0 methanol).

Example – 28

The purified salt (24 g) (example – 27) was stirred with 240 ml water and a solution of 3 g caustic soda in 30 ml water was added till pH = 11 was obtained. The reaction mixture was stirred for 10 min. and extracted with methylene chloride (100 ml + 50 ml). The combined extracts were washed with water 3 x 50 ml, dried over anhydrous sodium sulphate, and evaporated to dryness to give 12 g. product Sp. Rotation = + 29.4821 (c=1, 95% EtOH)

Example – 29

Venlafaxine base - 10 g as obtained in stage 28 was stirred with 100 ml acetone to this solution dry HCl gas was passed till pH = 2 is obtained. The suspension is then refluxed for 30 min. slowly cooled to 25 to 30 °C, and stirred for 1 hr. at 25 to 30 °C filtered, given acetone wash. Dried at 60 °C to a constant weight Dry 10.0 g Sp. Rotation = - 4.4928, (c=1, 95% EtOH)

Example – 30

(-) Venlafaxine HCl - 5 g as obtained in example 29 was refluxed with 75 ml isopropanol for 5 min. and then slowly cooled to 25 to 30 °C, stirred 1 hr at r.t., filtered, washed with 2 x 5 ml isopropanol, dried at 60 °C, dry weight = 3.9 gm, Sp. Rotation = - 4.46 (c=1, 95% EtOH)

Example – 31

The solvent was distilled in vacuum from the filtrate collected in (example 26) gave 40 g sticky residue, this was stirred with 150 ml methylene chloride and 400 ml water. To this a solution of 5 g NaOH in 50 ml water was added and stirred for 10 min. Organic layer was separated, aqueous layer was extracted with 150 ml methylene chloride combined organic layers are washed with water (2 x 50 ml) and the solvent was evaporated gave 18 g residue. Sp. Rotation = -24.80, (c = 1, 95% EtOH)

Example – 32

(-) Venlafaxine base 17 g as obtained in example 31 was dissolved in 85 ml ethylacetate. To this with stirring a solution of di-p-tolyl-L-tartaric acid (13.4 g) in ethylacetate (85 ml) was added in 30 min. at 25 to 30°C. The mass was stirred 1 hr at r.t., filtered and solid was washed with ethyl acetate (2 x 17 ml) wet = 43 g dried at 60 °C to a constant dry weight = 26 gm.

Example – 33

26 g salt as obtained in example 32 was stirred with 260 ml water and 100 ml methylene chloride. To this a solution of sodium hydroxide (3.3 g) in water (33 ml) was slowly added and stirred 15 min. more at 25 to 30°C. Aqueous layer was separated and extracted with 50 ml methylene chloride. The combined organic layers were washed with

water (2 x 50 ml) and the solvent was evaporated in vacuum to give 12.8 g product. Sp. Rotation = - 23.58 (c= 1, 95% EtOH)

Example – 34

5

(-)Venlafaxine base 10 g as obtained in example 33 was dissolved in 100 ml acetone. To this dry HCl gas was passed at 25 to 30 °C till pH = 2 was obtained. It was then refluxed for 5 min. and slowly cooled to 25 to 30 °C and stirred for 1 hr. at 25 to 30 °C. Solid was filtered, washed with acetone and dried at 60 °C dry weight = 9.3 gm, Sp. Rotation = +4.34 (c=1, 95% EtOH).

10

Example – 35

(+) Venlafaxine HCl (5 g) was refluxed with 75 ml isopropanol for 5 min. The solution was then slowly cooled to 25 to 30 °C and stirred for 1 hr at this temp., filtered, washed with isopropanol(2 x 5 ml), dried at 60°C, dry weight = 4.0 g.

15

WE CLAIM: -

1. Novel crystalline polymorphic forms of racemic Venlafaxine hydrochloride, i.e., Form-I, Form-II & Form-III and crystalline forms of R(+) and S(-) Venlafaxine hydrochloride.
5
2. Novel crystalline Form - I racemic Venlafaxine hydrochloride as claimed in claim - 1 and characterized by the following X-ray powder diffraction angles (2 θ): 6.79, 8.41, 10.27, 12.75, 13.54, 15.42, 15.58, 15.62, 15.74, 16.31, 16.35, 16.80, 18.99, 19.79, 20.35, 21.24, 21.82, 25.04, 25.09, 25.15, 27.22, 27.27, 28.47, 28.56, 28.61, 31.09, 31.59, 31.65, 31.72, 33.99, 35.12 and 35.23.
10
3. Novel crystalline Form - I racemic Venlafaxine hydrochloride according to claim - 1 and claim - 2 and further characterized by ¹³CP/MAS NMR spectra having chemical shifts in parts per million (ppm): 221.52, 197.24, 196.76, 193.64, 179.11, 171.72, 157.90, 133.62, 133.14, 130.04, 115.49, 108.10, 94.26, 74.11, 69.99, 69.51, 66.40, 59.36, 54.81, 51.84, 50.99, 44.45, 43.40, 42.37, 37.80, 35.69, 25.52 and 21.74.
15
4. Novel crystalline Form - II of racemic Venlafaxine hydrochloride as claimed in claim - 1 and characterized by the following X-ray powder diffraction angles (2 θ): 6.69, 10.21, 13.45, 15.31, 15.38, 15.52, 18.14, 18.17, 19.61, 19.68, 20.26, 21.46, 21.58, 21.65, 21.71, 22.57, 22.65, 25.49, 25.54, 27.16, 28.02, 28.10, 28.18, 28.21, 34.97 and 35.06.
20
5. Novel crystalline Form - II racemic Venlafaxine hydrochloride according to claim - 1 and claim - 4 and further characterized by ¹³CP/MAS NMR spectra having chemical shifts in parts per million (ppm): 221.28, 198.23, 196.18, 194.37, 181.35, 172.33, 157.65, 134.62, 132.58, 130.75, 117.74, 108.71, 94.03, 73.89, 71.00, 68.94, 67.11, 59.23, 55.59, 54.13, 51.32, 45.08, 43.29, 41.49, 37.80, 25.94, 23.74 and 21.40.
25
6. Novel crystalline Form - III of racemic Venlafaxine hydrochloride as claimed in claim - 1 and characterized by the following X-ray powder diffraction angles (2 θ): 6.73, 10.24, 13.49, 15.37, 15.41, 15.48, 15.56, 18.18, 18.22, 20.18, 20.30, 21.60, 21.65, 21.74, 27.20, 27.26, 35.09 and 35.18.
30
7. Novel crystalline Form - III racemic Venlafaxine hydrochloride according to claim - 1 and claim - 6 and further characterized by ¹³CP/MAS NMR spectra having chemical
35

shifts in parts per million (ppm): 221.27, 198.25, 196.20, 194.37, 181.38, 172.32, 157.66, 134.65, 132.59, 130.79, 117.77, 108.74, 94.04, 73.93, 71.01, 68.97, 67.15, 59.30, 55.63, 54.17, 51.36, 45.09, 43.33, 41.53, 37.85, 26.00, 23.84 and 21.45.

- 5 8. Crystalline form of R(+) Venlafaxine hydrochloride as claimed in claim -1 and further characterized by the following X-ray powder diffraction angles (2θ): 6.44, 8.45, 10.13, 12.29, 12.45, 12.90, 15.11, 16.4, 17.98, 18.19, 19.26, 19.43, 19.62, 20.97, 24.70, 25.46, 26.01, 27.65, 27.73, 32.68, 36.90 and 36.97.
- 10 9. Crystalline form of S(-) Venlafaxine hydrochloride as claimed in claim - 1 and further characterized by the following X-ray powder diffraction angles (2θ): 6.44, 8.45, 10.13, 12.29, 12.45, 12.90, 15.11, 16.4, 17.98, 18.19, 19.26, 19.43, 19.62, 20.97, 24.70, 25.46, 26.01, 27.65, 27.73, 32.68, 36.90 and 36.97.
- 15 10. A process for the preparation of polymorphic Form - I of Venlafaxine hydrochloride which comprises dissolving Venlafaxine base in an organic solvent selected from the group consisting of aliphatic ketones, aliphatic alkanols, aliphatic nitriles, aliphatic esters and aromatic hydrocarbons in the presence of anhydrous hydrogenchloride.
- 20 11. A process as claimed in claim 1 wherein said anhydrous hydrogenchloride is dry anhydrous hydrogenchloride gas.
12. A process as claimed in claim 10 or 11 wherein said aliphatic ketones is selected from acetone, methyl ethyl ketone and methyl isobutyl ketone.
- 25 13. A process as claimed in claim 10 or 11 wherein said aliphatic alkanol is selected from $C_1 - C_5$ straight or branched chain alkanol such as methanol, ethanol, n-propanol, isopropanol, n-butanol or tert-butanol.
- 30 14. A process as claimed in claim 10 or 11 wherein said aliphatic nitriles are selected from the group consisting of acetonitrile, propionitrile, butyronitrile and valeronitrile.
- 35 15. A process as claimed in claim 10 or 11 wherein said aliphatic esters are selected from the group consisting of methyl acetate, ethyl acetate, propyl acetate, butyl acetate and isopropyl acetate

16. A process as claimed in claim 10 or 11 wherein said aromatic hydrocarbons are selected from benzene, toluene and xylene.
- 5 17. A process as claimed in any one of claims 10 to 16 wherein the volume of solvents employed is from 2 to 30 times the volume of Venlafaxine base.
18. A process as claimed in claim 17 wherein said volume of said solvents is from 10 to 15 times the volume of Venlafaxine base.
- 10 19. A process as claimed in any one of claims 10 to 17 wherein the temperature of the solution of Venlafaxine base in said organic solvent is between -10°C to $+30^{\circ}\text{C}$ before the addition of anhydrous hydrogen chloride.
- 15 20. A process as claimed in claim 19 wherein the said temperature is from 0 to 20°C .
21. A process as claimed in claim 10 wherein said solvent is isopropanol and said solution of Venlafaxine base is treated with said anhydrous hydrogen chloride at the temperature in the range of 40 to 85°C .
- 20 22. A process as claimed in claim 21 where the said temperature is between 80 to 85°C .
23. A process as claimed in claim 21 or 22 wherein the Venlafaxine hydrochloride solution
25 formed is cooled to 0 to 50°C and then filtered.
24. A process as claimed in claim 23 wherein said temperature is reduced to 0 to 30°C before filtration.
- 30 25. A process for the preparation of polymorphic Form - I of Venlafaxine hydrochloride which comprises dissolving Form II or III of Venlafaxine hydrochloride in hot isopropanol, then cooling the solution to 0 to 50°C , filtering the product and drying the product so obtained.

26. A process as claimed in claim 25 wherein said reaction mixture is cooled to 0 to 30°C before said filtration
27. A process as claimed in claims 25 or 26 wherein the product is dried at 30 – 65°C,
5 preferably at 50°C.
28. A process as claimed in claim 25 wherein the volume of isopropanol employed is 5 to 20 times that of Venlafaxine hydrochloride Form II or Form III.
- 10 29. A process as claimed in claim 28 wherein the said volume is 10 to 15 times that of Venlafaxine hydrochloride Form II or Form III.
30. A process as claimed in any one of claims 25 to 29 wherein said hot isopropanol is at a temperature of from 50 to 85°C.
- 15 31. A process as claimed in any one of claims 30 wherein said temperature is 65 to 85°C.
32. A process for the preparation of polymorphic Form II of Venlafaxine hydrochloride
20 which comprises treating Venlafaxine base in with a solvent selected from acetone, ethyl acetate, acetonitrile and MIBK and passing dry hydrogen chloride gas at 0 to 35 °C, refluxing for 15 to 60 minutes, cooling the reaction mixture to a temperature of 0 to 55°C, filtering the product and drying it at 40 – 85°C.
- 25 33. A process as claimed in claim 32 wherein said dry hydrogen chloride gas is passed at a temperature of 25 to 30°C, said refluxing is carried out for 1 hr, the reaction mixture is cooled to 30 to 35°C, filtering and the filtered product is dried at 50 to 55°C.
- 30 34. A process of preparing polymorphic Form II of Venlafaxine hydrochloride which comprises dissolving polymorphic Form I of Venlafaxine hydrochloride in methanol, removing methanol to dryness and recovering the material or after removing methanol, adding acetone, refluxing for 15 to 90 minutes, preferably for 60 minutes, cooling to 0 to 45 °C, preferably to 25 to 35 °C, filtering and drying the product at 50 to 85 °C, preferably to 50 to 60°C.
- 35

35. A process as claimed in claim 34 wherein said refluxing is for 60 minutes, said cooling is 25 to 35 °C, and the filtered product is dried at 50 to 60°C.
36. A process of preparing polymorphic Form III of Venlafaxine hydrochloride which
5 comprises dissolving Form I of Venlafaxine hydrochloride in methanol, removing methanol to dryness, adding acetone, refluxing acetone, cooling to 0 to 35°C, preferably to 5 to 10°C, centrifuging, drying at 55 to 75 °C, preferably at 55°C on 10 to 50 kg on plant scale.
- 10 37. A process of preparing polymorphic Form – III of Venlafaxine hydrochloride which comprises dissolving Venlafaxine base in toluene and adding a solution of HCl gas in IPA and heating the resulting mixture to 50 to 115°C, and cooling to –10 to +50 °C and drying at 50 to 75 °C.
- 15 38. A process as claimed in claim 37 wherein said reaction mixture is heated at reflux temperature and cooled 25 to 35 °C and dried at 50 to 60 °C.
39. A process as claimed in claim – 16 provides the methods of the preparations of all the three forms of racemic Venlafaxine hydrochloride in pure form by changing the reaction
20 conditions.
40. A process as claimed in claim – 39 wherein the said solvent employed is toluene.
41. A process as claimed in claim 39 and 40 wherein racemic Venlafaxine base is dissolved
25 in 5 – 25 volumes of toluene, preferably 10 volumes of toluene for the preparation of all the three forms of racemic Venlafaxine hydrochloride.
42. A process as claimed in claim – 41 wherein Form – I is produced by passing dry hydrogen chloride gas to the toluene solution of racemic Venlafaxine base at 0 – 5 °C,
30 filtering and drying the product.
43. A process as claimed in claim – 41 wherein Form – II is prepared by passing dry hydrogen chloride gas to the toluene solution of racemic Venlafaxine base at 20 – 50°C, preferably at 30 – 35 °C , refluxing the solution, cooling the product at 25 – 55°C,
35 preferably at 30 – 35 °C , filtering and drying the product.

44. A process as claimed in claim – 41 wherein Form – III is prepared by adding isopropanolic hydrogen chloride gas solution, refluxing and cooling the product at 25 – 55 °C, preferably at 30 – 35 °C, filtering and drying the product.

45. A process for the preparation of a compound of formula I which comprises condensing p-methoxy phenyl acetonitrile with cyclohexanone in the presence of alkali/alkali earth metal hydroxide.

46. A process as claimed in claim 45 wherein said alkali/alkali earth metal hydroxide is selected from the group consisting of lithium hydroxide, sodium hydroxide or potassium hydroxide.

47. A process as claimed in claim 46 wherein sodium hydroxide is used in molar ratio of 1 to 5.

48. A process as claimed in claim 47 wherein sodium hydroxide employed is in molar ratio of 3.

49. A process as claimed in any one of claims 45 to 48 wherein said condensation is effected in the presence of a co-solvent.

50. A process as claimed in claim 49 wherein said co-solvent is a C₂ to C₄ normal or branched chain alkanols selected from the group consisting of ethanol, n-propanol, isopropanol, n-butanol, isobutanol and tert. butanol.

51. A process as claimed in claim 50 wherein said co-solvent is tert-butanol employed in a molar ratio of 0.5 to 5

52. A process as claimed in claim 51 wherein said tert-butanol is used in molar ratio of 1.1

53. A process as claimed in any one of claims 45 to 52 wherein said condensation is achieved in a mixture of aliphatic and aromatic hydrocarbons.

54. A process as claimed in claim 53 wherein said aliphatic hydrocarbon is normal or branched chain C₃ to C₁₀ selected from n-pentane, n-hexane, n-heptane, n-octane and isooctane.
- 5 55. A process as claimed in claim 53 wherein said aromatic hydrocarbon is selected from benzene, toluene, ortho-, meta-, para xylene.
56. A process as claimed in claim 53 to 55 wherein said aliphatic hydrocarbon is n-hexane and aromatic hydrocarbon is toluene.
- 10 57. A process as claimed in claim 56 wherein a mixture of n-hexane and toluene is used in a ratio of 90 : 10 to 50 : 50 v/v.
58. A process as claimed in claim 57 wherein ratio of n-hexane to toluene is 85 : 15 v/v.
- 15 59. A process as claimed in claim 58 wherein said mixture employed is 5 to 20 volumes of p-methoxy phenyl acetonitrile.
60. A process as claimed in claim 59 wherein said mixture employed is 10.7 volume of p-methoxyphenyl acetonitrile.
- 20 61. A process as claimed in any one of claims 45 to 60 wherein the molar ratio of cyclohexanone is 1 to 2.
- 25 62. A process as claimed in claim 61 wherein the molar ratio of cyclohexanone is 1.1.
63. A process as claimed any one of claims 45 to 62 wherein said condensation reaction is carried out a temperature of from -20 to +25 °C.
- 30 64. A process as claimed in claim 63 wherein said reaction temperature is -5 to -10 °C.
65. A process for the preparation of a compound of formula II of hydrogenation a compound of formula I so that cyano group thereof is reduced to an amino methyl group, wherein said hydrogenation is carried out in the presence of activated (Raney) metals such as cobalt, Nickel and copper.
- 35

66. A process as claimed in claim 65 wherein said Raney metal is a Raney Nickel which is used in an amount 0.25 to 1 times w/w as that of compound of formula I.
- 5 67. A process as claimed in claim 66 wherein said Raney Nickel employed is 0.5 times w/w as that of compound of formula I
68. A process as claimed in any one of claims 65 to 67 wherein said hydrogenation is carried out in the presence of anhydrous ammonia employed in an amount of from 0.25
10 to 1 times w/w as that of compound of formula I.
69. A process as claimed in claim 66 wherein said amount of anhydrous ammonia is 0.5 times w/w as that of compound of formula I.
- 15 70. A process as claimed in any one of claims 65 to 69 wherein said hydrogenation is carried out on the presence of a solvent selected from ethanol, n-propanol, isopropanol, methanol, n-butanol isobutanol, tert-butanol and ethyl acetate.
71. A process as claimed in claim 70 wherein the amount of said solvent is 5 to 25 volumes
20 of that said compound of formula I.
72. A process as claimed in claim 71 wherein the amount of said solvent is 15 times the volume of said compound of formula I.
- 25 73. A process as claimed in any one of claims 65 to 72 wherein said hydrogenation is performed at the pressure of 30 to 90 psi.
74. A process as claimed in claim 73 wherein said pressure for hydrogenation reaction is 60
30 psi.

Fig - 1

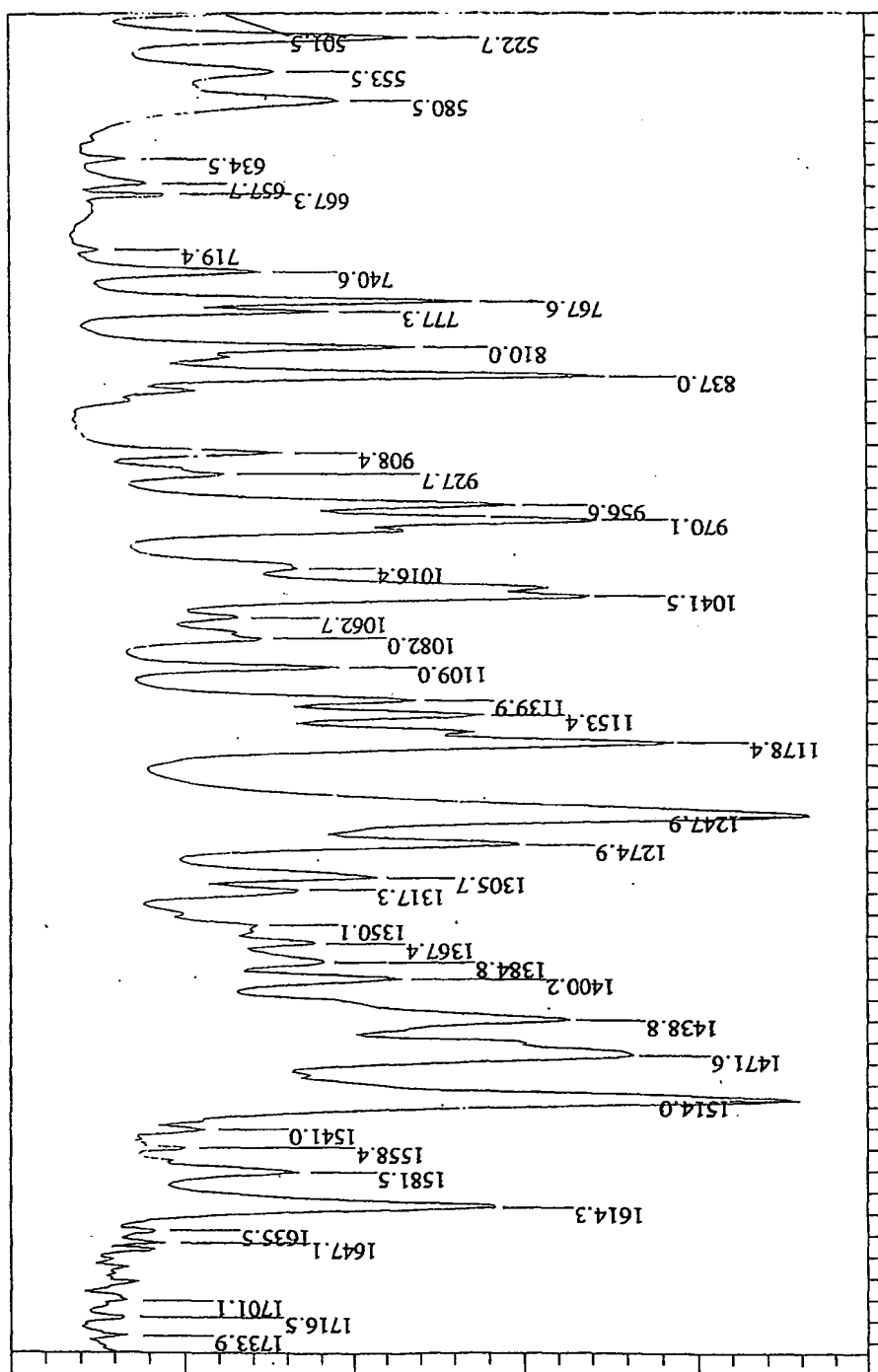


Fig - 2

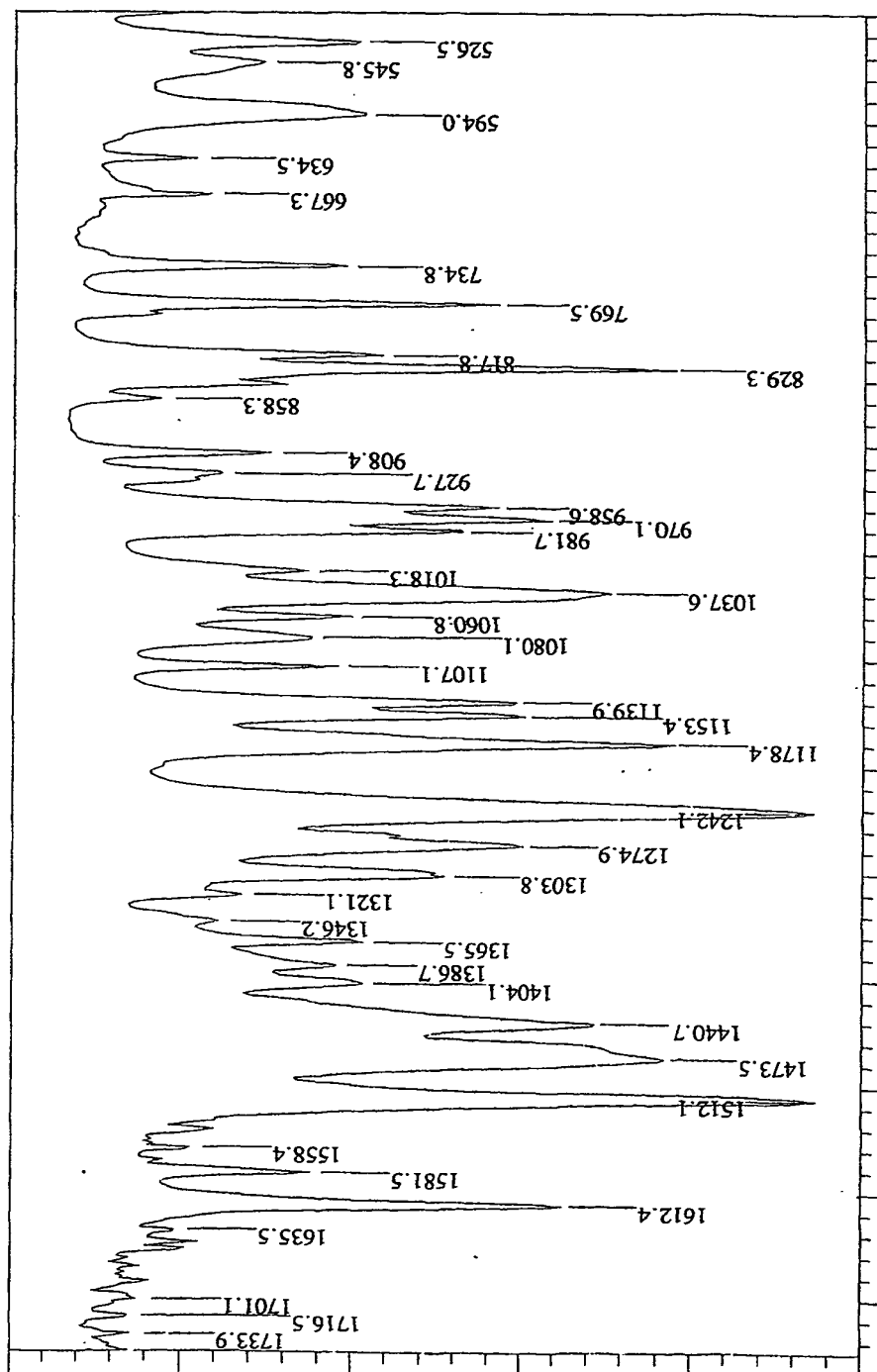


Fig - 3

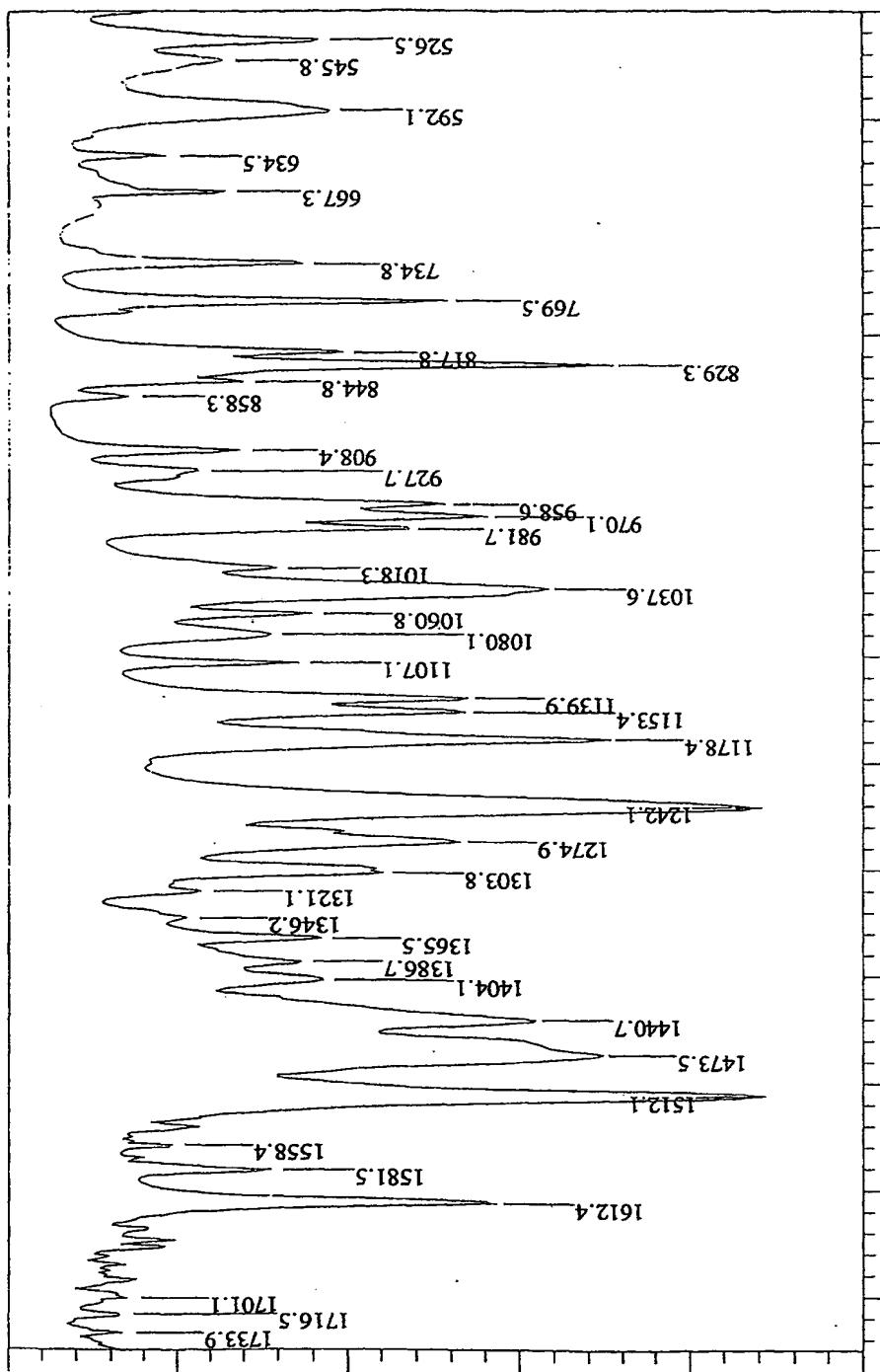


Fig - 4

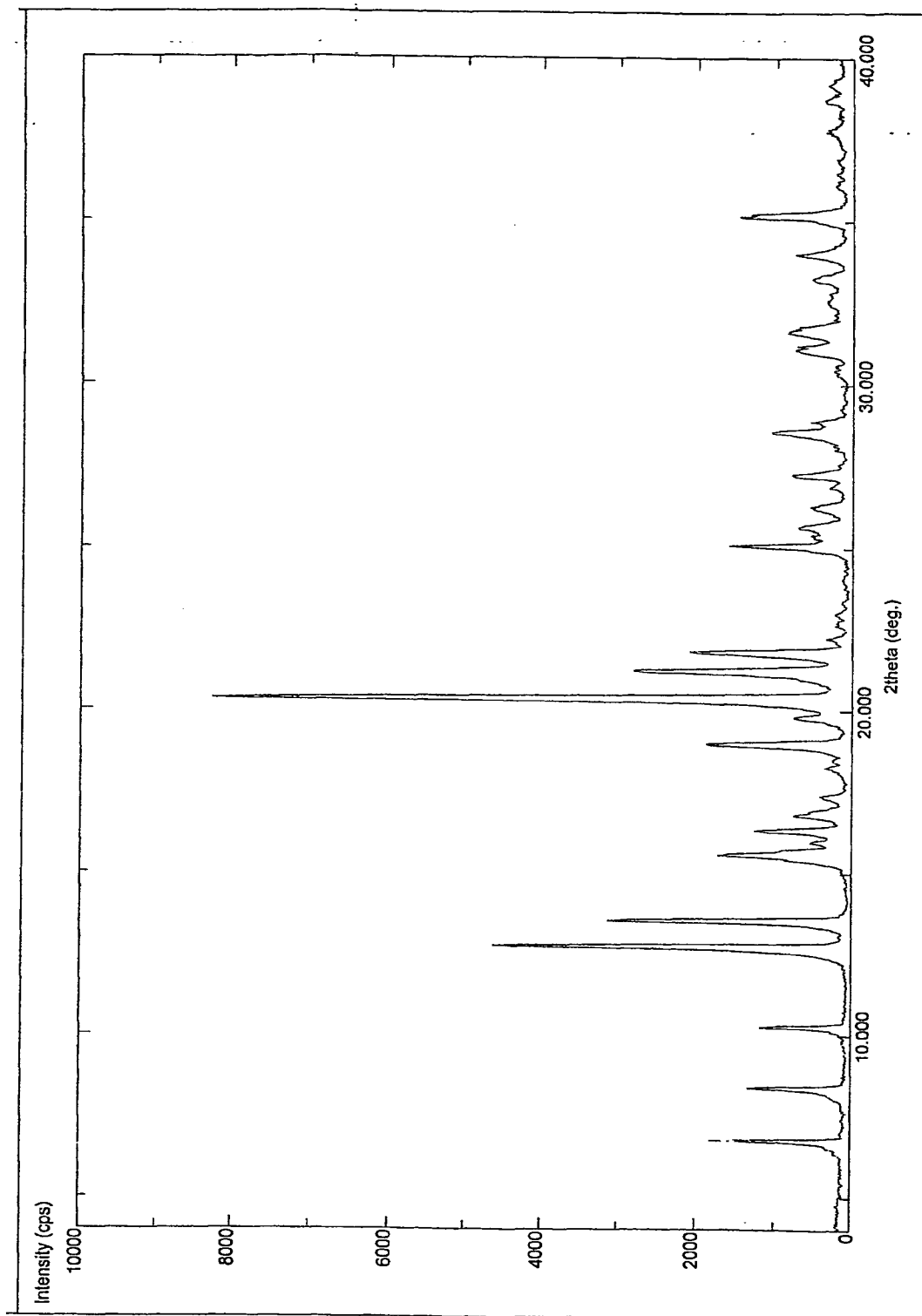


Fig - 5

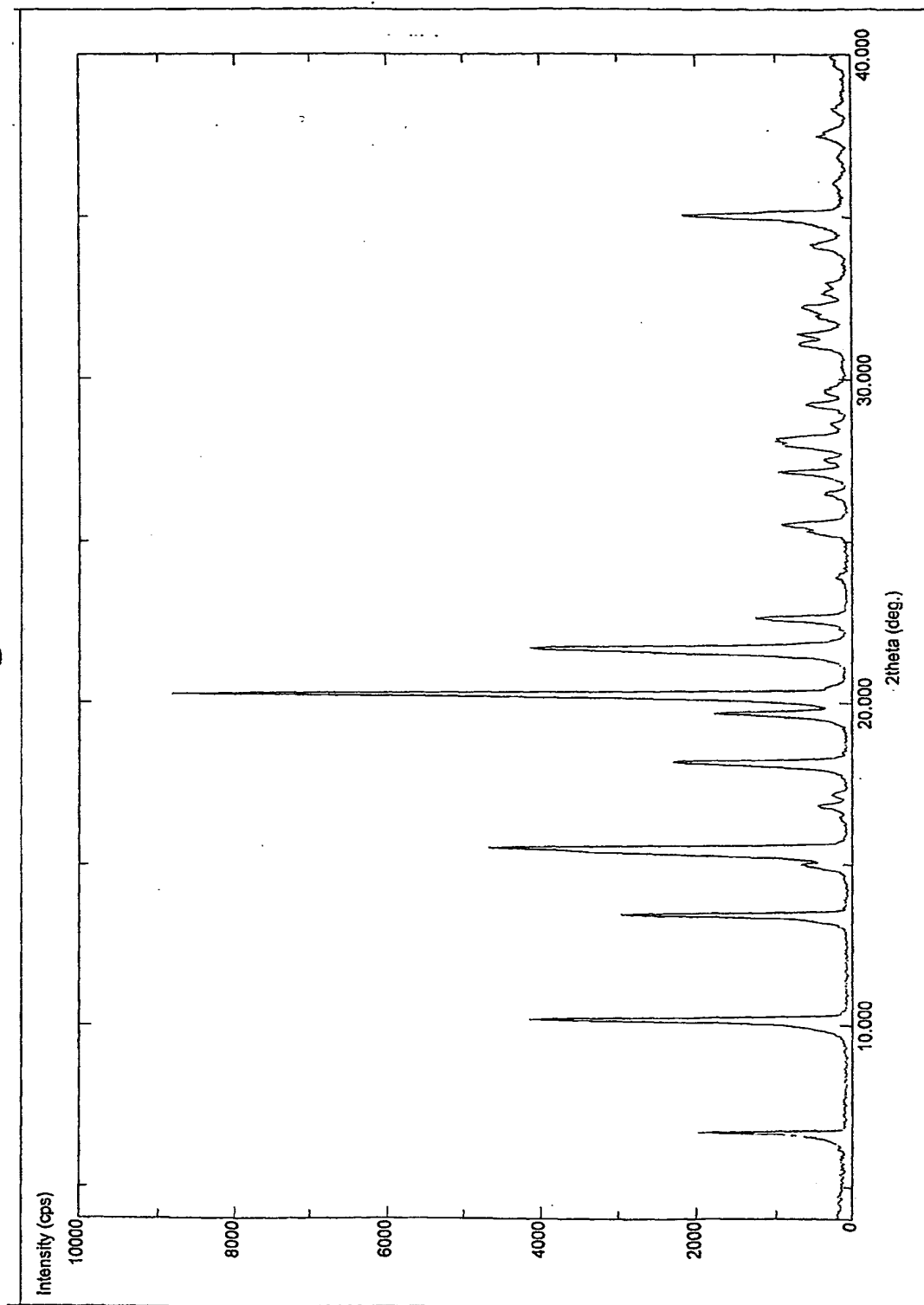


Fig - 6

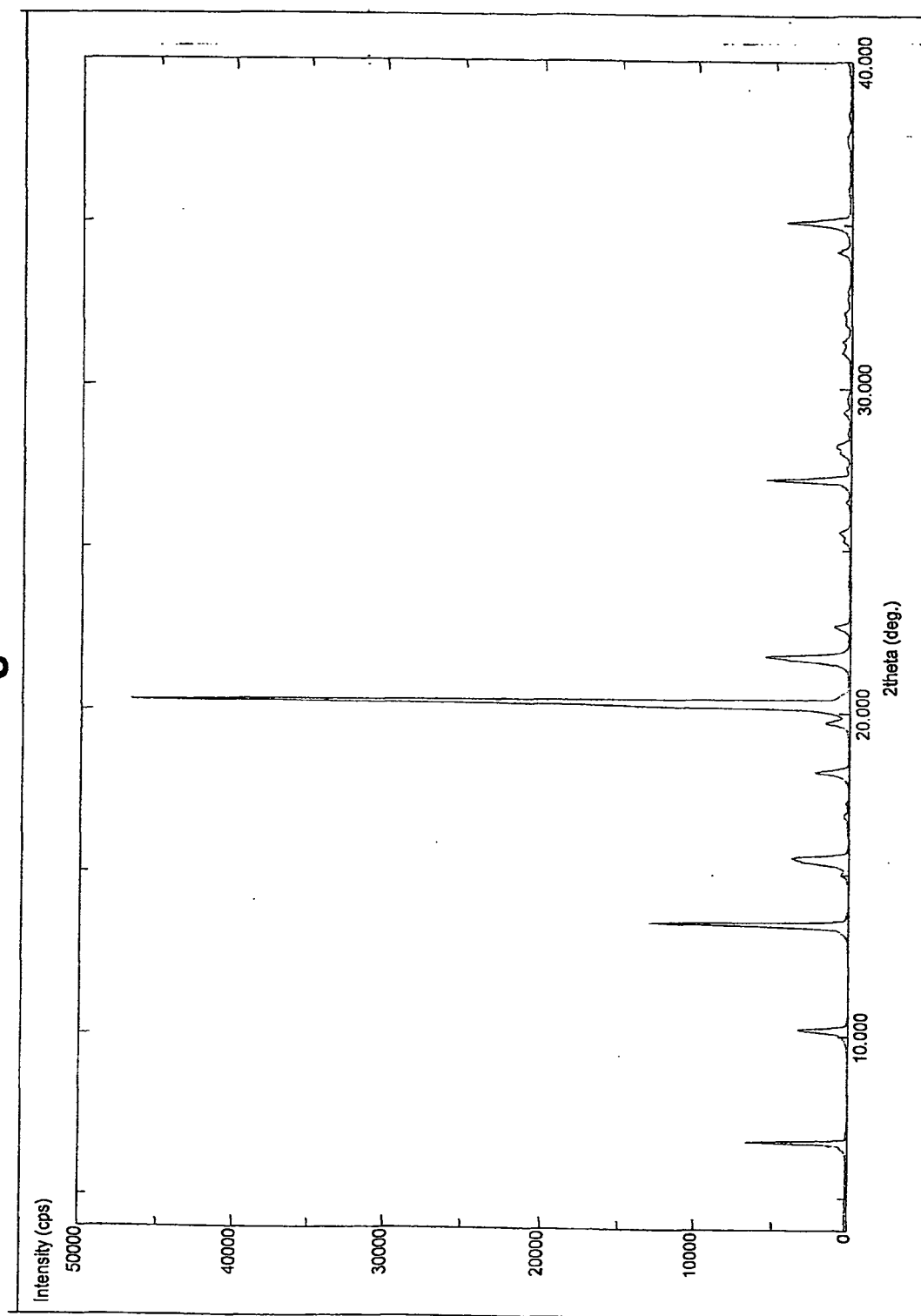


Fig - 7

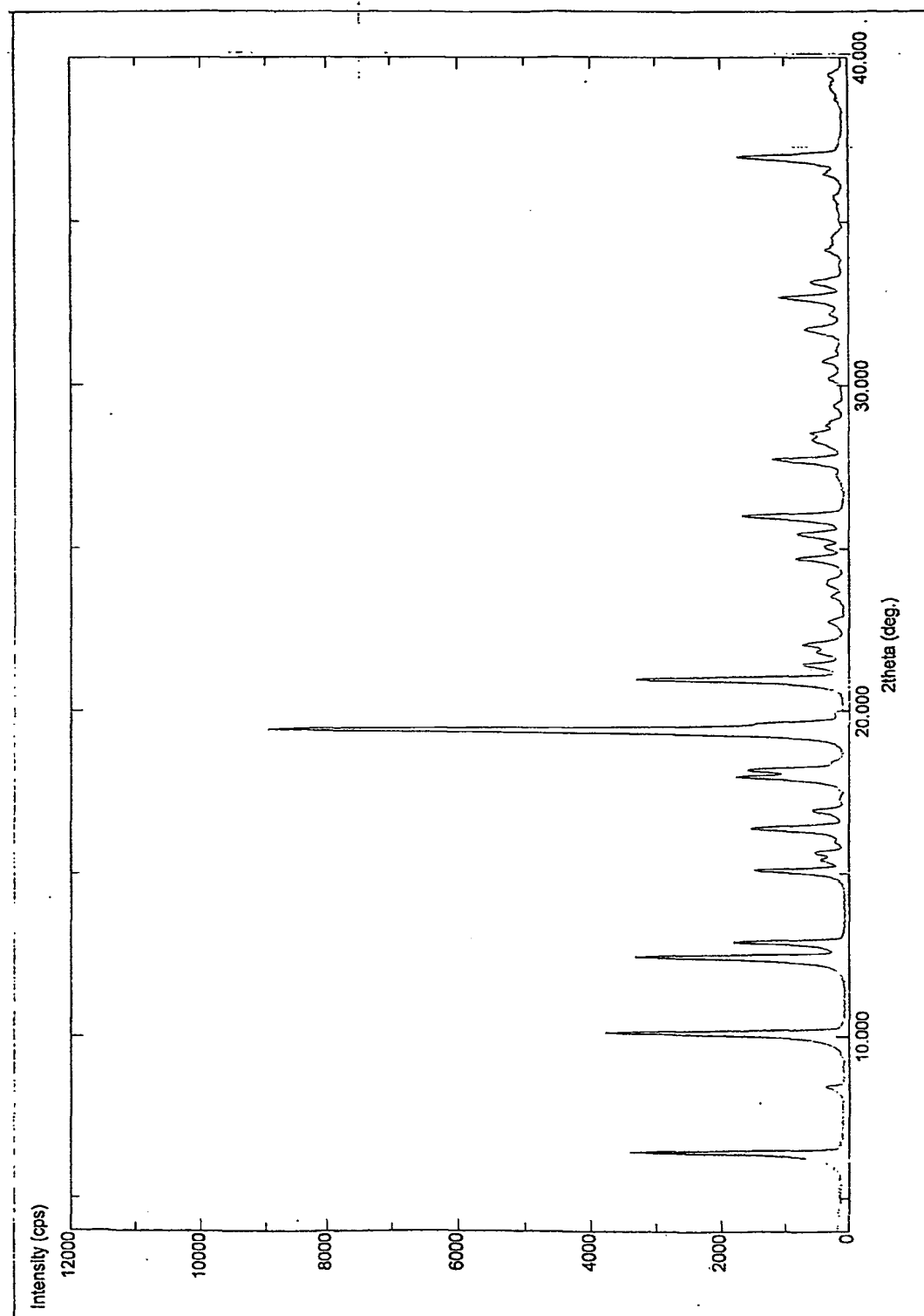


Fig - 8

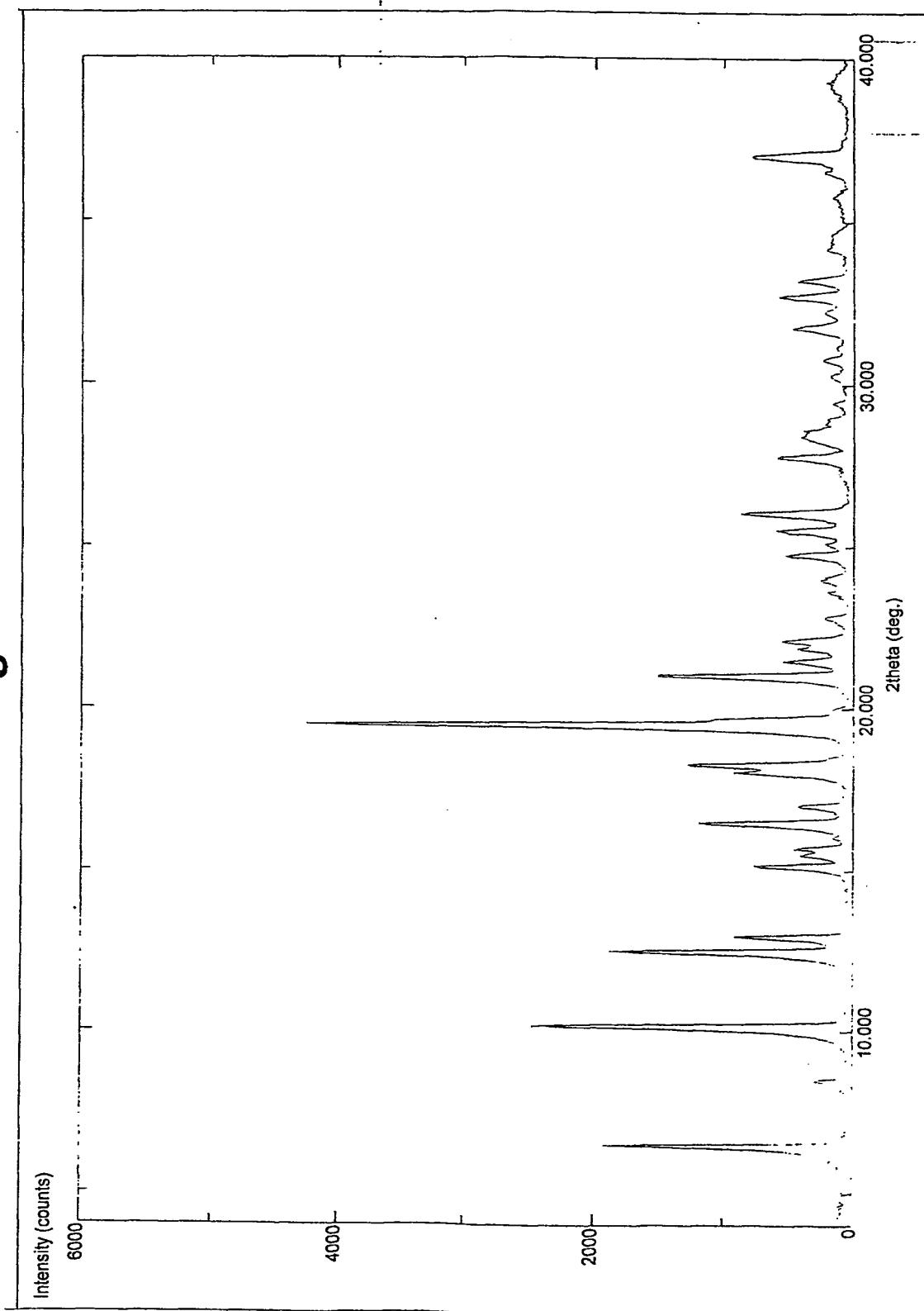


Fig - 9

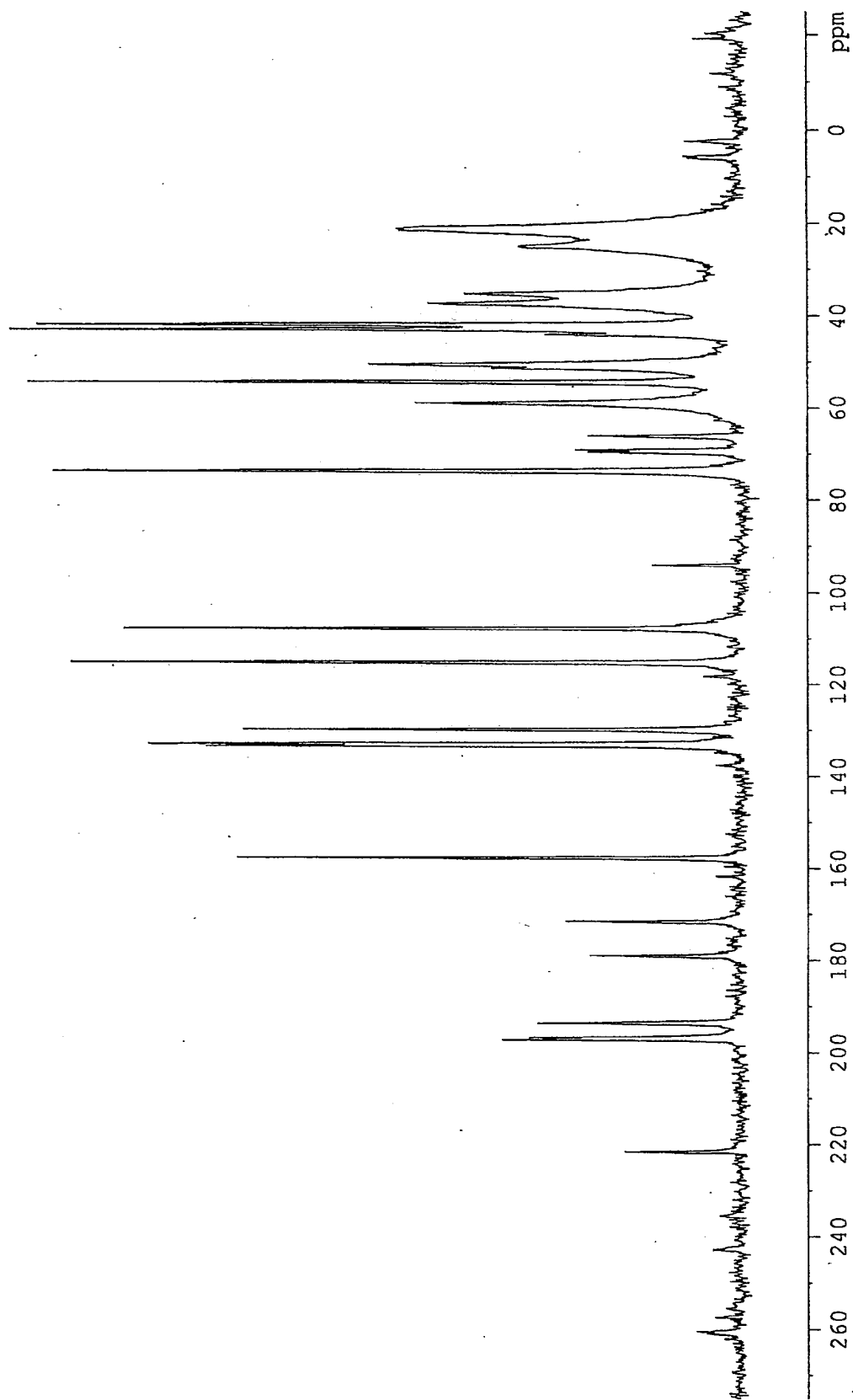


Fig - 10

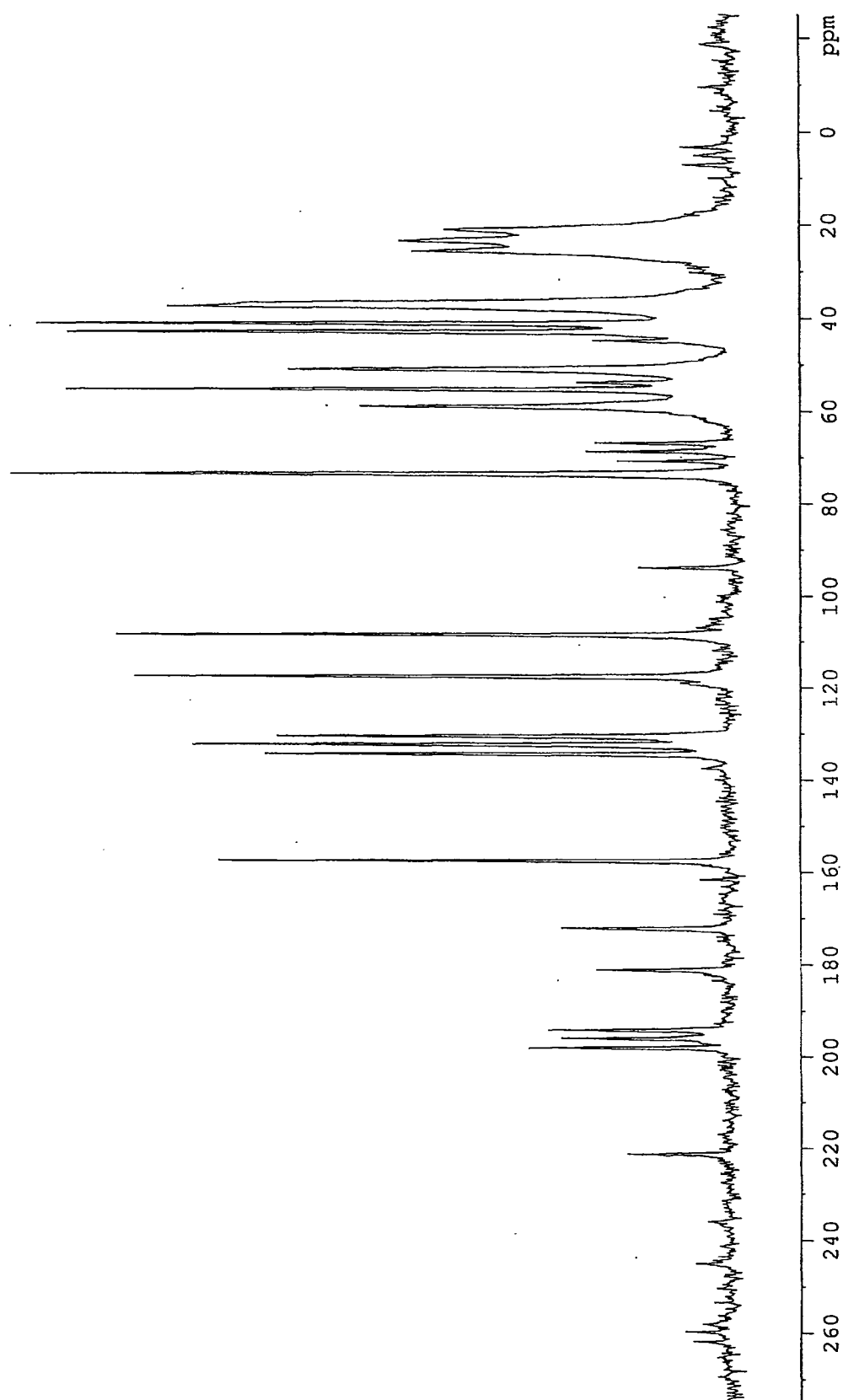


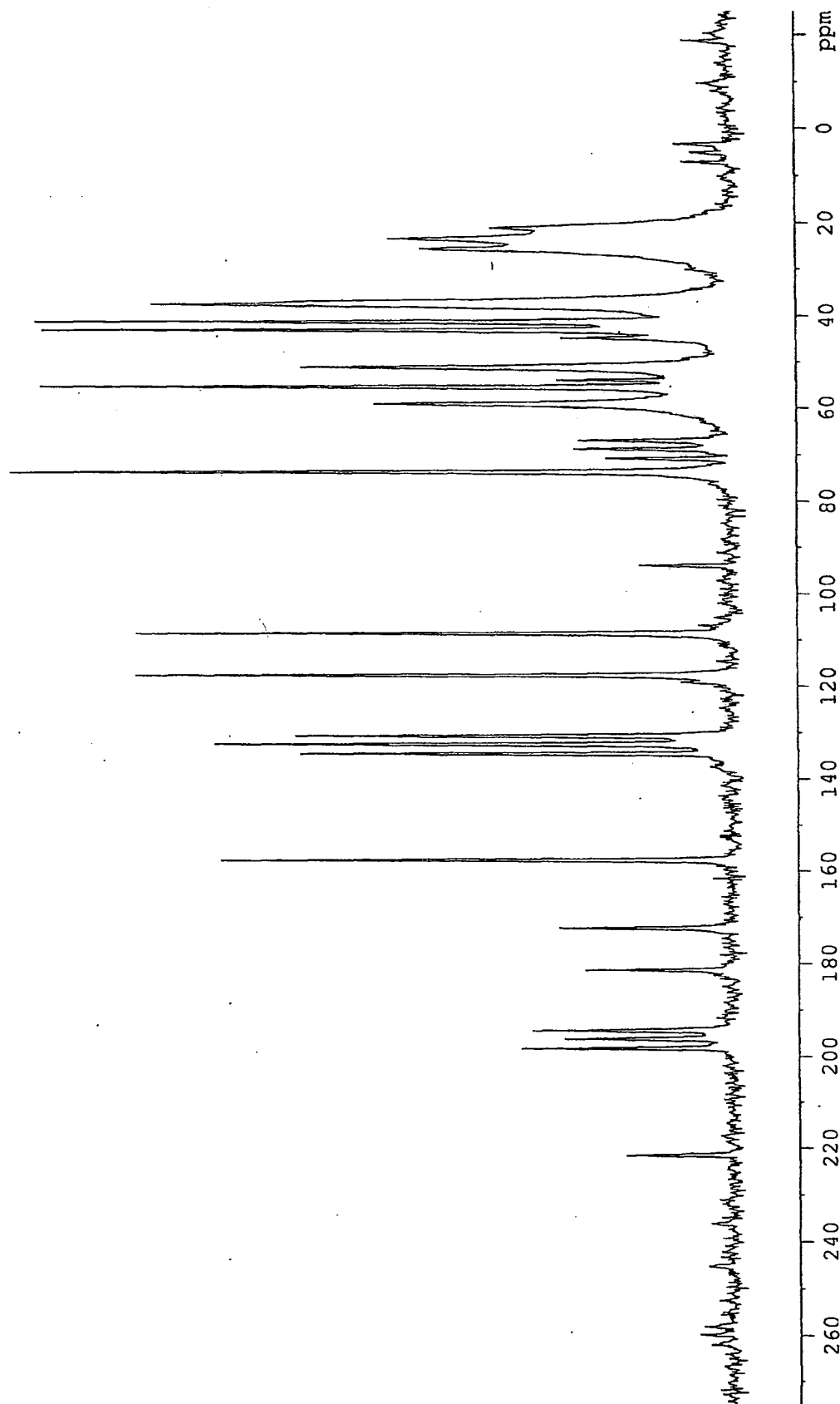
Fig - 11

Fig - 12

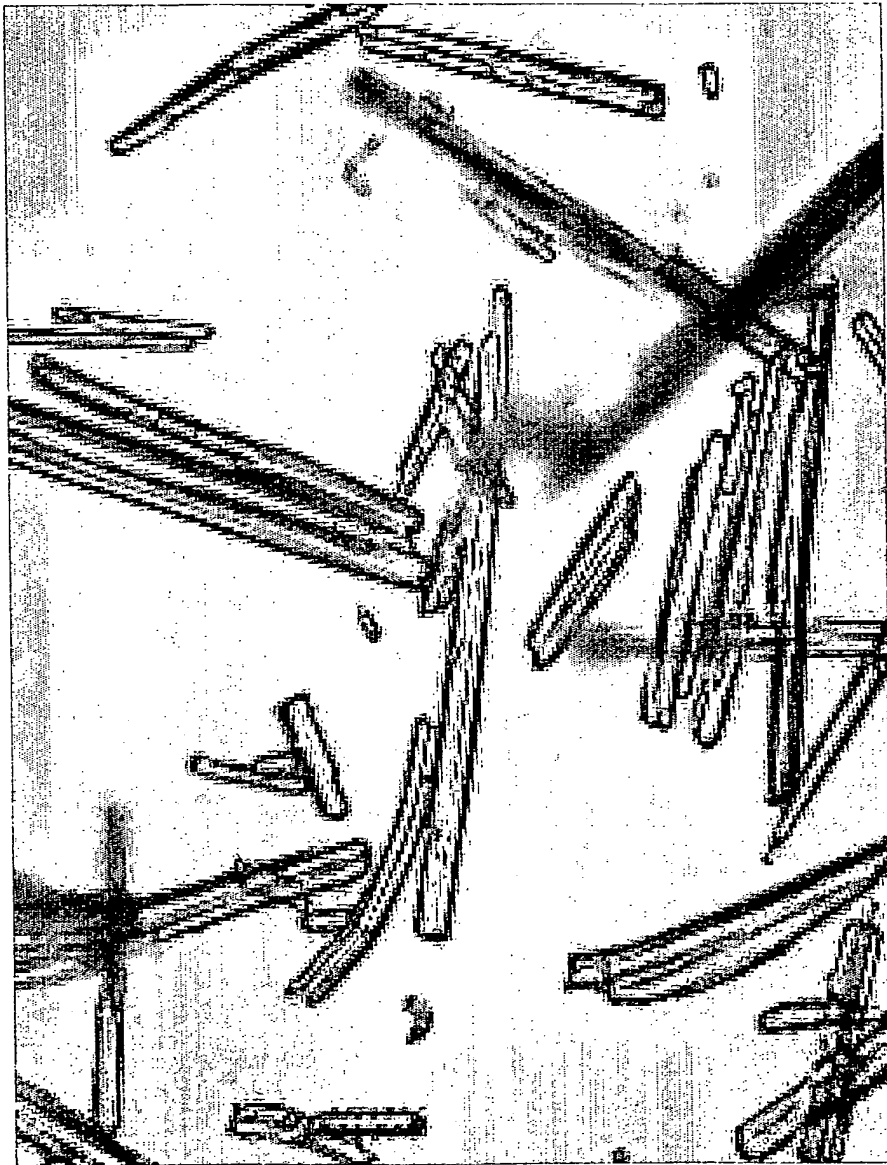


Fig - 13

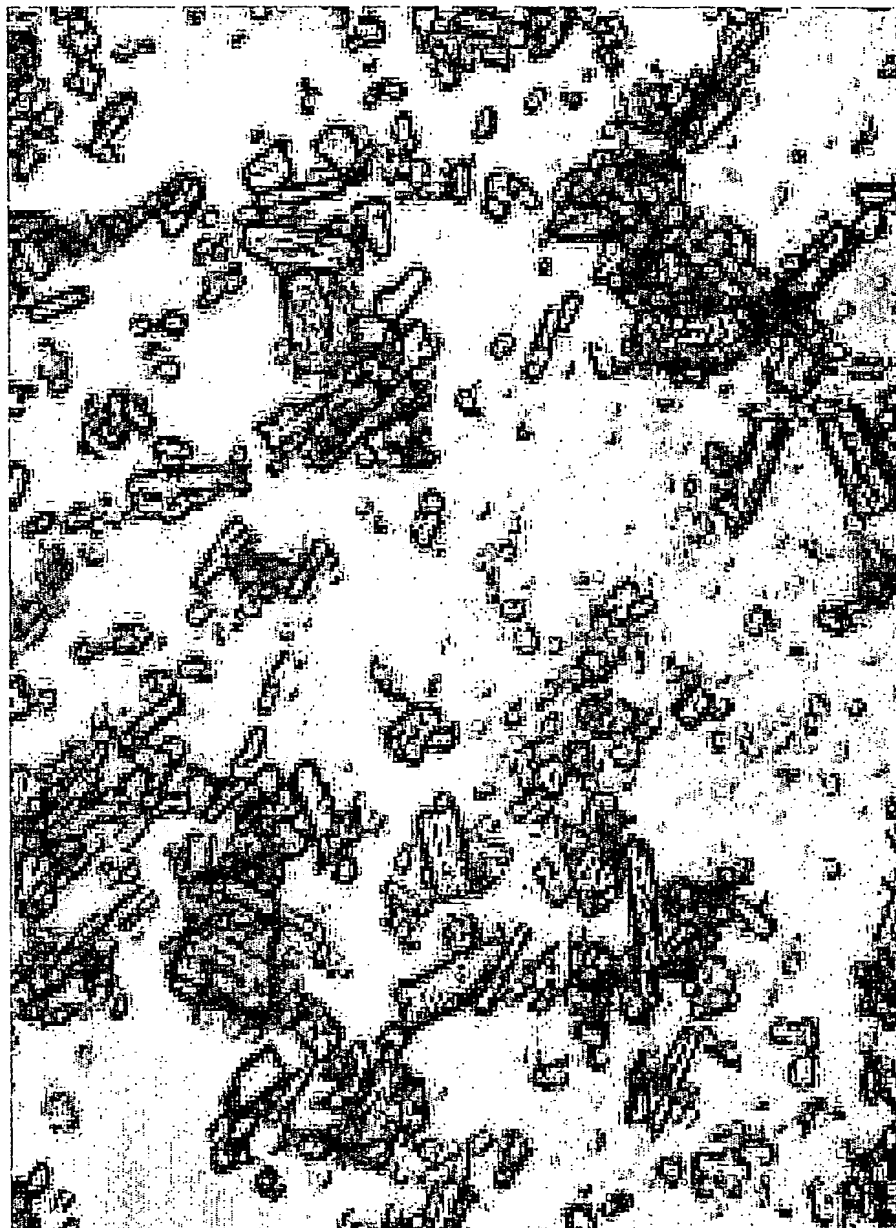
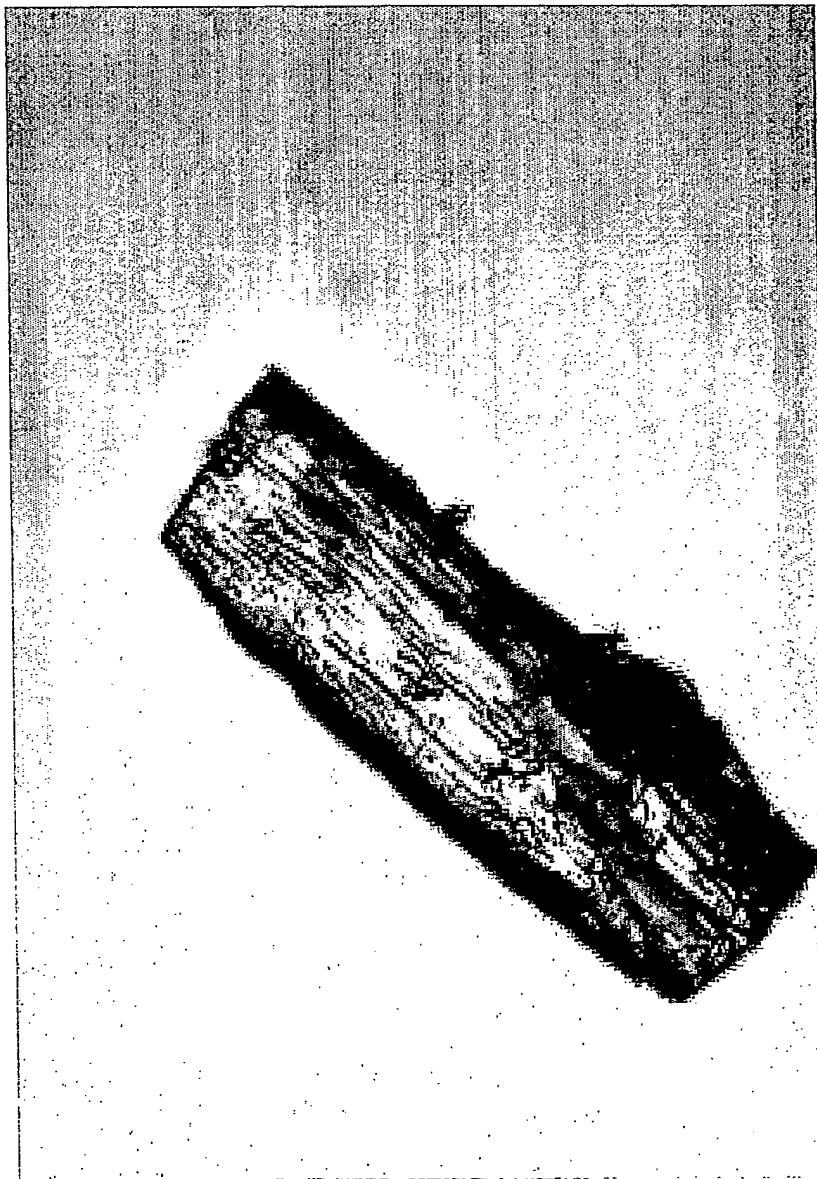


Fig – 14



INTERNATIONAL SEARCH REPORT

 International Application No
 PCT/IN 02/00046

 A. CLASSIFICATION OF SUBJECT MATTER
 IPC 7 C07C217/74 C07C213/10 C07C213/02 C07C253/30

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

 Minimum documentation searched (classification system followed by classification symbols)
 IPC 7 C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

WPI Data, PAJ, EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
E	WO 02 36542 A (CIBA SC HOLDING) 10 May 2002 (2002-05-10) the whole document ---	1-7,25, 26,28, 30,31
E	WO 02 46140 A (DR. REDDY RESEARCH FOUNDATION) 13 June 2002 (2002-06-13) the whole document ---	1-7
E	WO 02 45658 A (TEVA PHARMA) 13 June 2002 (2002-06-13) the whole document ---	1-7, 10-12, 17,19,20
	--- -/--	

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
 "E" earlier document but published on or after the international filing date
 "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
 "O" document referring to an oral disclosure, use, exhibition or other means
 "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
 "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
 "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
 "&" document member of the same patent family

Date of the actual completion of the international search

16 August 2002

Date of mailing of the international search report

28. 11. 2002

Name and mailing address of the ISA

 European Patent Office, P.B. 5818 Patentlaan 2
 NL - 2280 HV Rijswijk
 Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
 Fax: (+31-70) 340-3016

Authorized officer

Krische, D

INTERNATIONAL SEARCH REPORT

 International Application No
 PCT/IN 02/00046

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	YARDLEY J P ET AL: "2-PHENYL-2-(1-HYDROXYCYCLOALKYL)ETHYLAMIN E DERIVATIVES: SYNTHESIS AND ANTIDEPRESSANT ACTIVITY" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY, WASHINGTON, US, vol. 33, 1990, pages 2899-2905, XP000891765 ISSN: 0022-2623 cited in the application page 2900 -page 2902 page 2904 tab.I, cpd.4, scheme I ---	1,8,9
X	VEGA, DANIEL ET AL.: ACTA CRYSTALLOGRAPHICA, vol. C56, 2000, pages 1009-1010, XP001040413 the whole document ---	1
X	WO 99 22724 A (AMERICAN HOME PROD) 14 May 1999 (1999-05-14) page 4, line 10 - line 18 ---	1
X	DATABASE CA [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; retrieved from STN Database accession no. 133:252074/DN, HCAPLUS XP002210065 abstract & CN 1 240 206 A (HUADONG SCIENCE AND ENGINEERING UNIV.) 5 January 2000 (2000-01-05) ---	1,10,11, 13
X	US 4 761 501 A (HUSBANDS, G E MORRIS ET AL) 2 August 1988 (1988-08-02) cited in the application abstract; examples 1-3 -----	1,10,13

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IN 02/00046

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-44

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-44

Crystalline forms of Venlafaxine hydrochloride and processes for their preparation

2. Claims: 45-64

Process for the preparation of a compound of formula I

3. Claims: 65-74

Process for the preparation of a compound of formula II

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/IN 02/00046

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 0236542	A	10-05-2002	AU 1234002 A WO 0236542 A1	15-05-2002 10-05-2002
WO 0246140	A	13-06-2002	WO 0246140 A1 AU 3597001 A	13-06-2002 18-06-2002
WO 0245658	A	13-06-2002	AU 4176402 A WO 0245658 A2 US 2002143211 A1	18-06-2002 13-06-2002 03-10-2002
WO 9922724	A	14-05-1999	AU 747978 B2 AU 1300399 A BG 104397 A BR 9813179 A CA 2305242 A1 CN 1278165 T CZ 20001659 A3 EE 200000212 A EP 1028718 A2 HR 20000213 A1 HU 0004287 A2 JP 2001521892 T NO 20002126 A PL 341141 A1 SK 6472000 A3 TR 200001232 T2 WO 9922724 A2 US 6274171 B1 US 2001055612 A1 US 2002025339 A1 ZA 9810081 A	30-05-2002 24-05-1999 28-02-2001 22-08-2000 14-05-1999 27-12-2000 17-10-2001 16-04-2001 23-08-2000 31-12-2000 29-04-2002 13-11-2001 04-05-2000 26-03-2001 07-11-2000 21-12-2000 14-05-1999 14-08-2001 27-12-2001 28-02-2002 04-05-2000
CN 1240206	A	05-01-2000	NONE	
US 4761501	A	02-08-1988	US 4535186 A AT 28628 T AU 567524 B2 BG 60659 B2 CA 1248540 A1 DE 3372753 D1 DK 571383 A ,B, EG 17630 A EP 0112669 A2 ES 527938 D0 ES 8702336 A1 ES 544402 D0 ES 8802131 A1 FI 834523 A ,B, GB 2133788 A ,B GB 2173787 A ,B GR 79750 A1 IE 56324 B1 IL 70390 A JP 1823303 C JP 3178953 A JP 5030826 B JP 1762120 C JP 3135948 A	13-08-1985 15-08-1987 26-11-1987 30-11-1995 10-01-1989 03-09-1987 14-06-1984 30-06-1992 04-07-1984 01-01-1987 16-03-1987 01-04-1988 16-06-1988 14-06-1984 01-08-1984 22-10-1986 31-10-1984 19-06-1991 31-12-1986 10-02-1994 02-08-1991 11-05-1993 28-05-1993 10-06-1991

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/IN 02/00046

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 4761501	A	JP 4040339 B	02-07-1992
		KR 9100436 B1	25-01-1991
		LU 88750 A9	23-08-1996
		MX 155545 A	25-03-1988
		PH 20074 A	18-09-1986
		PT 77771 A ,B	01-01-1984
		US 4611078 A	09-09-1986
